Supplementary File

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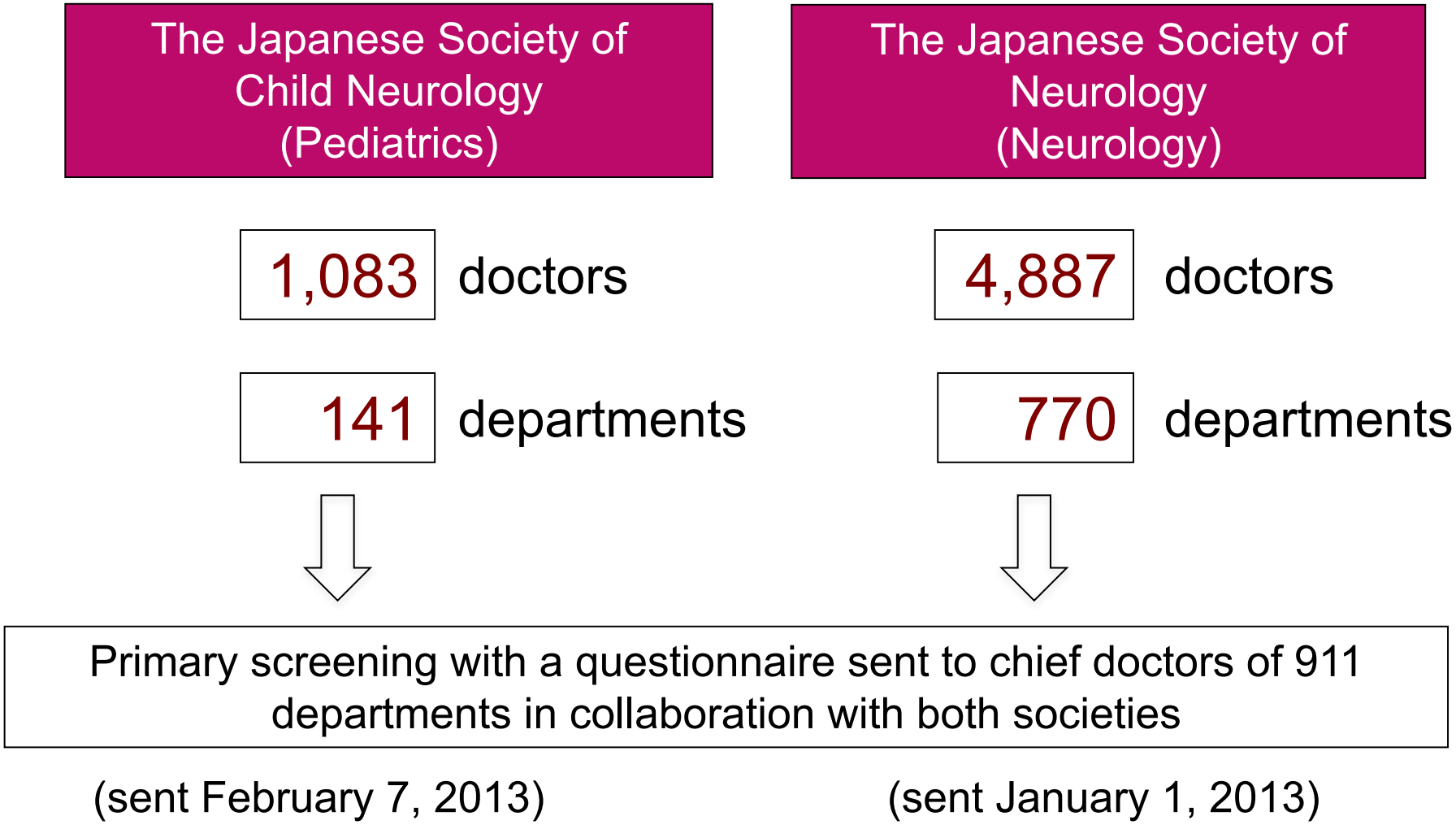
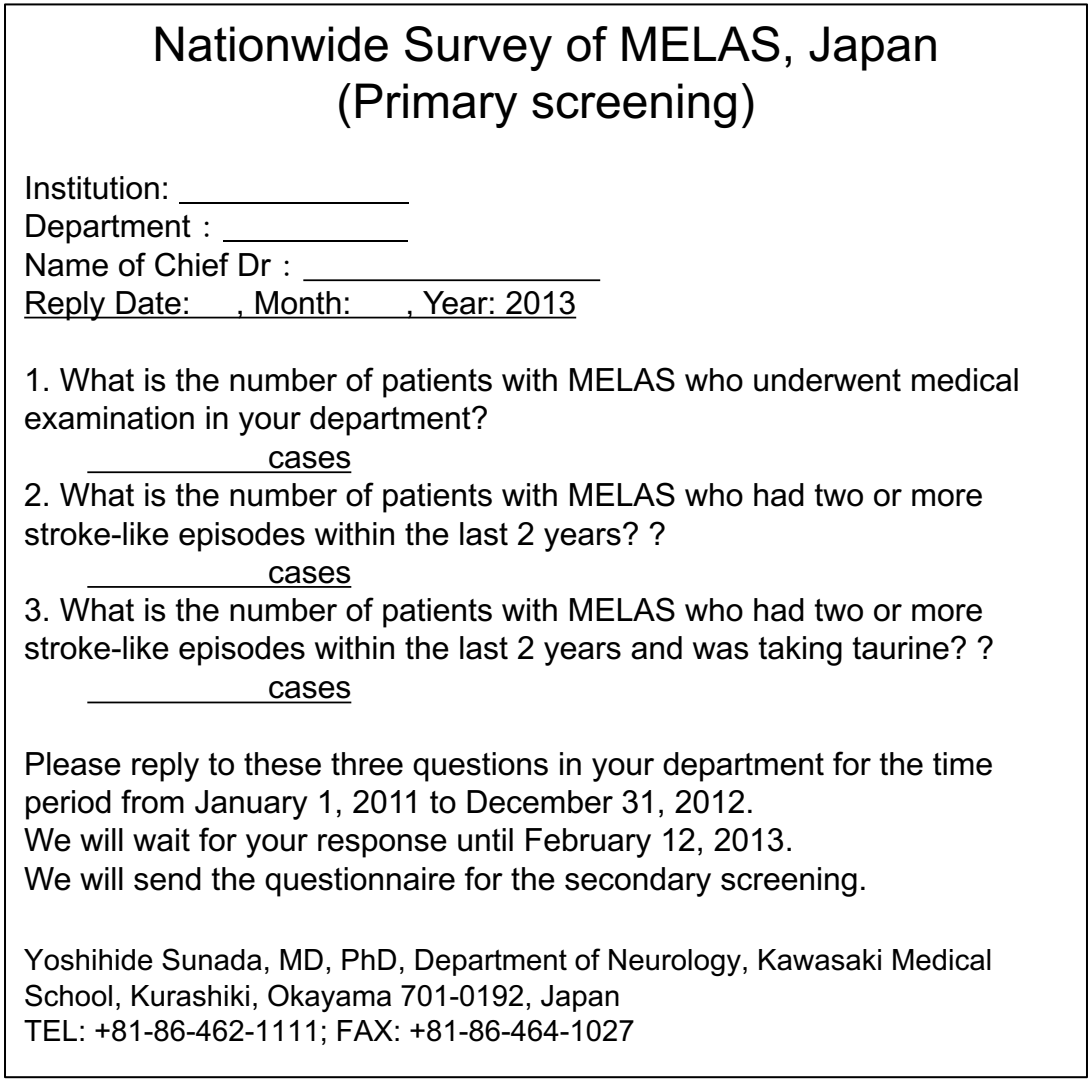


Figure S1 Nationwide survey of MELAS across Japan. The primary screening was initiated by a questionnaire on patients with MELAS sent to 911 clinical departments (770 adult neurology departments, 141 pediatric neurology departments) in collaboration with the Japanese Society of Neurology and the Japanese Society of Pediatric Neurology.



Nationwide Survey of MELAS, Japan
(Primary screening)

Institution: _____
Department : _____
Name of Chief Dr : _____
Reply Date: , Month: , Year: 2013

1. What is the number of patients with MELAS who underwent medical examination in your department?
_____cases
2. What is the number of patients with MELAS who had two or more stroke-like episodes within the last 2 years? ?
_____cases
3. What is the number of patients with MELAS who had two or more stroke-like episodes within the last 2 years and was taking taurine? ?
_____cases

Please reply to these three questions in your department for the time period from January 1, 2011 to December 31, 2012.
We will wait for your response until February 12, 2013.
We will send the questionnaire for the secondary screening.

Yoshihide Sunada, MD, PhD, Department of Neurology, Kawasaki Medical School, Kurashiki, Okayama 701-0192, Japan
TEL: +81-86-462-1111; FAX: +81-86-464-1027

Figure S2 Primary screening. The questionnaire sent to all clinical departments during the primary screening. Information on patients with MELAS was collected. Patients with less than two stroke-like episodes within the two-year period before screening and those taking taurine supplementation were excluded.

Nationwide Survey of MELAS, Japan
(Secondary screening)

Institution: _____ Department : _____
Name of Chief Dr : _____
e-mail address: _____
Reply Date: , Month: , Year: 2013

Please answer the questions below regarding patients with MELAS who had two or more stroke-like episodes within the last 2 years.

Category A

- ☐ Was he/she conclusively diagnosed with MELAS by diagnostic criteria based on clinical manifestations, muscle biopsy, and genetic testing?
- ☐ Does he/she harbor either 3243A>G, 23271T>G, 3244G>A, 3258T>C, or 3291T>C mutation in mitochondrial DNA? Type of point mutation:
- ☐ Did he/she have two or more stroke-like episodes within the last year? How many times? _____ times.
- ☐ Has he/she taken taurine so far? Is he/she eligible for neurological examinations and brain MRI in your department?

Category B

- ☐ Does he/she have status epilepticus or deep coma?
- ☐ Is he/she unable to communicate effectively due to severe dementia or long-term bed-ridden status?
- ☐ Does he/she have sepsis?
- ☐ Does he/she have a past history of drug allergy?
- ☐ Does he/she have severe medical conditions, including heart, liver, or renal failure?
- ☐ Does he/she need to be administered oral glucocorticoids for more than 2 weeks?
- ☐ Does he/she take L-Arginine?
- ☐ Does he/she take pyruvate?
- ☐ Is she pregnant? Is she lactating?
- ☐ Has he/she been enrolled in other clinical trials within the past 3 months?

Special Remarks:

Please return this questionnaire before March 18, 2013.
Yoshihide Sunada, MD, PhD, Department of Neurology, Kawasaki Medical School, Kurashiki, Okayama 701-0192, Japan
TEL: +81-86-462-1111; FAX: +81-86-464-1027

Figure S3 Secondary screening. The detailed questionnaire during the second screening of patients with more than two stroke-like episodes within the two-year period before screening.

Nationwide Survey of MELAS, Japan
(Tertiary Screening)

Institution: _____ **Department :** _____

Name of Chief Dr : _____ **e-mail :** _____

Please inform us about the patient as described in the secondary screening. Please fulfill each check box.

Patient (Initial) _____ ・ _____

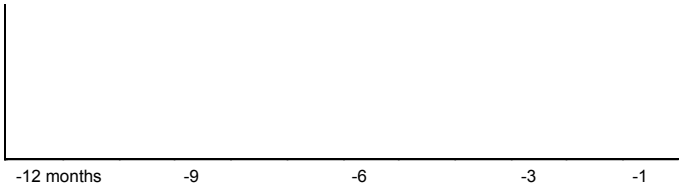
Gender：□ male □ female age：( ) years old.

Questions about the patient

1. The type of mutation in the mitochondrial DNA.
   □A3243G □G3244A □T3258C □T3291C

2. Does your department store the description of the DNA testing?
   - □ Stored
   - □ Not stored, but available
   - □ Not stored, not available (Information alone)

3. Please describe the below chart about the onset and the neurological symptoms of stroke-like episodes in the patient within recent 12 months.
   ①hemiparesis or monoparesis ②cortical sensory disturbance（sensory extinction）
   ③cortical visual disturbance（scintillation, cortical blindness）④aphasia ⑤apraxia ⑥agnosia
   ⑦headache ⑧nausea, vomiting ⑨epilepsy ⑩consciousness disturbance



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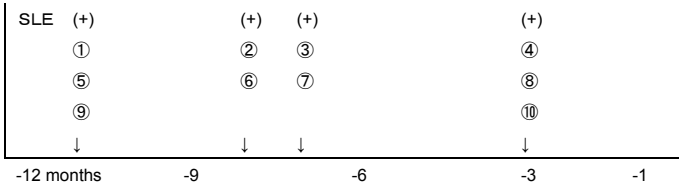
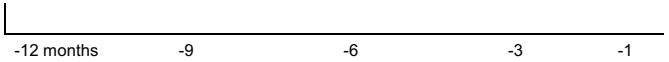


4. Did you check brain MRI in the patient within recent 12 months?（ □ Yes □ No ）
   If Yes, please describe the time when you check brain MRI.



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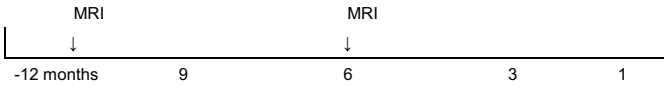

5. Was the patient administered oral L-Arginine within recent 12 months?（ □ Yes □ No ）
   If Yes, please describe the term and the dose of L-Arginine!

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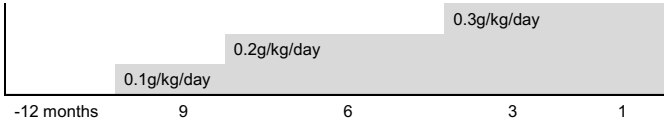

Questions about the institution

1. Can the local ethical committee of your institution discuss our investigator-initiated clinical trial until August, 2013? （ □ Yes □ No ）
2. Have you participated investigator-initiated clinical trial so far?（ □ Yes □ No ）

Special Remarks： _____

Description：Date: , Month: , Year: 2013

Yoshihide Sunada, MDS. PhD, Department of Neurology,Kawasaki Medical Scool, Kurashiki, Okayama 701-0192, Japan

TEL:+81-86-462-1111. FAX: +81-86-464-1027.

Please reply until May 5, 2013!

Figure S4 Tertiary screening. The questionnaire assessed the precise profile of stroke-like episodes and the simultaneous MRI examinations in patients with MELAS.

Table S1 Frequency of focal neurological deficits during the pretrial period

Patient No.	Duration (weeks)	Stroke-like episodes*	Stroke-like episodes* confirmed by the presence of MRI abnormalities
1	49	3	3
2	66	2	2
3	56	6	6
4	78	2	0
5	78	4	3
6	78	3	2
7	78	3	2
8	78	4	1
9	78	2	1
10	78	4	0
Total		33	20

*Stroke-like episodes during the pretrial period were not necessarily confirmed by magnetic resonance imaging (MRI)

Table S2 Frequency of focal neurological deficits during the evaluation period

Patient No.	Duration (weeks)	Stroke-like episodes confirmed by the presence of MRI abnormalities	Focal neurological deficits without MRI abnormalities	Total number of focal neurological deficits
1	52	0	0	0
2	52	1	0	1
3	52	0	0	0
4	52	1	0	1
5	52	0	1	1
6	52	0	0	0
7	52	0	1	1
8	52	1	0	1
9	52	0	0	0
10	52	1	0	1
Total		4	2	6

The Primer Extension/Taurine Modification of mitochondrial tRNA$^{Leu(UUR)}$

(1) Reagents

M-MLV Reverse Transcriptase (200 U/μL) (Thermo Fisher Scientific, Waltham, MA, USA; cat# 28025-013),

5× buffer (250 mM Tris-HCl pH 8.3, 375 mM KCl, 15 mM $MgCl_2$) and 0.1 M DTT

RNase inhibitor: RNaseOUT (Thermo Fisher Scientific, cat#10777-019) or rRNasein (Toyobo, Osaka, Japan; cat# SIN-201)

dATP/ddGTP mix: 1.5 mM dATP, 1.5 mM dTTP, 1.5 mM ddGTP

T4 Polynucleotide kinase (PNK. NEB, Ipswich, MA, USA; cat# M0201S) includes 10× buffer (700 mM Tris-HCl pH 7.6,

100 mM $MgCl_2$, 50 mM DTT)

[γ-^{32}P]ATP (6,000 Ci/mmol) (Perkin Elmer, Waltham, MA, USA; cat# NEG502Z, 37 MBq)

Primer W3243PM: 5'-acctctgactgtaaag-3'

3271PM: 5'-acctctgactgtaagg-3'

3280PM: 5'-acctccgactgtaaag-3'

2× ProK buffer: 20 mM Tris pH 8.0, 100 mM NaCl, 10 mM EDTA, 1% SDS

2× Loading dye

40% Acrylamide/Bis mixed (37.5:1) (Nacalai, Kyoto, Japan; cat# 06121-95)

Urea (Nacalai, cat# 35940-65)

10× TBE

10% APS

TEMED

(2) 5' end labeling Primer

Add to Eppendorf tube (0.5 mL)

Primer 10 μM	1 μL
sdH_2O	13 μL
10× T4 kinase buffer	2 μL
[γ-^{32}P]ATP (6,000 Ci/mmol)	3 μL
T4 PNK	1 μL
	20 μL

Incubate at 37°C for 1 h

Add 2× ProK buffer, 280 μL and 2 mg/mL glycogen, 2 μL

Phenol/CIAA

EtoH ppt

Rinse and dry up

Resuspend in 1× TE 100uL (final, 80–100 fmol/μL)

(3) Primer extension

Add to Eppendorf tube (0.5 mL)

A4 cybrid total RNA (1 μg/μL)	1 μL		
A3243G cybrid total RNA (1 μg/μL)		1μL	
Subject total RNA (0.5-1μg/μL)			1 μL
^{32}P-labbeled primer 100 fmol/μL	2 μL	2 μL	2 μL
1× TE	5 μL	5 μL	5 μL
	8 μL	8 μL	8 μL

Heat at 80°C for 2 min, then place tubes at room temperature for 5 min–1 h

To another tube, add:

	Per reaction	_____ x reaction
sdH_2O	4.5 μL	μL
5× RT buffer	4 μL	μL
0.1M DTT	1 μL	μL
dATP/ddGTP mix	0.5 μL	μL
RNasein	1 μL	μL
M-MLV	1 μL	μL
	12 μL	μL

Mix well and spin down

Dispense 12 μL of the RT mix into each tube containing annealed primer/RNA

Incubate 42°C for 1 h

Add 2× loading dye, 20 μL

Store at −20°C or load 2 μL of sample per lane of an acrylamide gel

(4) Preparation of 7 M Urea/15% Acrylamide Gels

Use glass plate (20 cm × 40 cm) and shark comb

Clean glass plate very thoroughly.

Urea	21 g
10× TBE	5 mL
sdH_2O	10 mL
40% Acrylamide	18.75 mL
Total volume	50 mL

Heat at 60°C for 20 min

Degas the mixture

Cool down on ice

Add 10% APS, 250 μL and TEMED, 25 μL

Cast the gel and let polymerize for at least 1 h

Pre-run the gel at 1200 V, 10 min

Load 2 μL of sample per lane.

Run 1500 V for 2 h

Fix the gel in 10% methanol/10% acetic acid for 10 min

Carefully place the gel on a stack of Whatmann paper.

Dry the gel for 1–2 h

Visualize the bands by autoradiography

Protocol and Statistical Analysis Plan

For the KN01 trial (UMIN000011908):

KN01 Multicenter Trial Focusing on

Mitochondrial Encephalomyopathy (MELAS)

Clinical Trial Protocol

Coordinating Investigator

Kawasaki Medical School

Department of Neurology

Sunada Yoshihide

Date of Creation: 7/24/2013

Clinical Trial Protocol Number: KN01-MELAS-01

Version Number: Version 1.0

Table of Contents

1. Summary of Clinical Trial Protocol

Trial title	KN01 Multicenter Trial Focusing on Mitochondrial Encephalomyopathy (MELAS)
Objective	Implementation of taurine therapy as a suppressive treatment for recurrent stroke-like episodes in MELAS patients and an examination of its efficacy and safety.
Subjects	Patients that meet all of the following inclusion criteria and do not violate the exclusion criteria.
Inclusion criteria	(1) Patients with a comprehensive and definitive diagnosis of MELAS who meet the criteria for MELAS based on clinical manifestations, muscle pathology, and genetic screening. (2) Patients who show any of the following point mutations in mitochondrial DNA: A3243G, T3271C, G3244A, T3258C, or T3291C. (3) Age, gender, and hospitalization/outpatient status will not be inquired at the time of consent. (4) Patients who have not used L-arginine within the 78-week period before consent is obtained or those who have been using L-arginine for a minimum of 26 weeks prior to consent. (5) Patients who meet the following criteria for stroke-like episodes* before consent is obtained: ① Patients who are not using L-arginine: at least two stroke-like episodes within the 78-week period before consent and at least one

	stoke-like episode within the 52-week period before consent are obtained. ② Patients who are using L-arginine and meet any of the following criteria during the period of L-arginine use: (i) If the period of L-arginine use is 78 weeks or less, at least two stroke-like episodes within that period and at least one stroke-like episode within the 52-week period before consent is obtained. (ii) If the period of L-arginine use is more than 78 weeks, at least two stroke-like episodes within the 78-week period before consent and at least one stroke-like episode within the 52-week period before consent is obtained. *A stroke-like episode for the selection criteria is defined as the presence of any of the following abrupt-onset focal neurological neurological deficits (with no consideration of brain magnetic resonance imaging [MRI] use): ① Hemiparesis or monoparesis ② Cortical sensory deficit (extinction) ③ Cortical visual deficit (scintillating scotoma or cortical blindness) ④ Aphasia ⑤ Apraxia ⑥ Agnosia

	(6) Patients with no history of oral taurine treatment. (7) Patients capable of judging the clinical manifestations of a stroke-like episode. (8) Individuals for whom informed consent for participation in this clinical trial is obtained in writing by the patients themselves before enrollment. (For minors, individuals for whom written consent is obtained from a legal guardian, and written assent is obtained from the patient themselves for participation in this clinical trial).
Exclusion criteria	(1) Patients who cannot undergo brain MRI, such as those with pacemakers. (2) Patients with status epilepticus or those in severe coma. (3) Patients with dementia, those who are bedridden, or those with whom communication is not possible. (4) Patients with concomitant sepsis. (5) Patients with severely impaired cardiac, hepatic, or renal function. (6) Patients who require systemic administration of steroids for 2 weeks or longer. (7) Patients who have used pyruvic acid within the 12-month

<table>
<tr><td></td><td>period before consent is obtained.
(8) Patients who are breast feeding, pregnant, or may become pregnant.
(9) Patients with a history of hypersensitivity to the components of the study drug.
(10) Patients with a history of drug allergies.
(11) Patients who have participated in a clinical trial within the 12-month period before consent is obtained.
(12) Patients who are determined to be ineligible as subjects for other reasons by the principal investigator or sub-investigator.</td></tr>
<tr><td>Target number of subjects</td><td>15 subjects.</td></tr>
<tr><td>The study drug</td><td>(1) Clinical study drug ID: KN01
(2) Generic name: Taurine
(3) Ingredients and dosage form: 1 g of taurine in 1.02 g powder</td></tr>
<tr><td>Dosage and administration method</td><td>The daily amount of the study drug, determined by patient body weight categories below, will be administered orally three times daily after meals.
<table><tr><td>Weight*</td><td>Amount per day</td></tr><tr><td>40 kg or more</td><td>12 g</td></tr><tr><td>25–39 kg</td><td>9 g</td></tr><tr><td>15–24 kg</td><td>6 g</td></tr><tr><td>Less than 15 kg</td><td>3 g</td></tr></table>* Body weight before the observation period</td></tr>
</table>

Administration period	52 weeks
Disallowed concomitant treatments and drugs	(1) Pyruvic acid, (2) steroids with systemic administration for 2 weeks or longer, and (3) oral L-arginine (in patients who are not taking oral L-arginine at the start of the clinical trial)
Allowed concomitant drugs	(1) Medications that the principal investigator or sub-investigator determine to be necessary may be used. However, the medication name, dosage and administration method, administration period, and reason for concomitance will be described in the case report. (2) Emergency treatment drugs: no limit (includes intravenous L-arginine). (3) Drugs that can be used during the trial period with limited changes to the dosage and administration: nitric acid, vasodilators with nitric oxide inducers, coenzyme Q, antiepileptic drugs (if taken continuously since the pretrial period), and oral L-arginine (if taken for 26 weeks or more before consent is obtained).
Observation, examination, and examination items	(1) Clinical symptoms (number of stroke-like episodes and mitochondrial disease severity score) (2) Physical examination (weight, temperature, blood pressure, and pulse) (3) Blood tests (hematological tests and biochemical examinations) (4) Specialized blood tests: Blood lactate (deproteinized), blood pyruvic acid

	(deproteinized), and blood amino acid analysis (39 types) Cerebrospinal fluid (CSF) examination (optional): CSF lactate (deproteinized), CSF pyruvic acid (deproteinized), and CSF amino acid analysis (39 types) Blood leukocyte examination (optional): Mitochondrial gene mutation rate, $tRNA^{Leu(UUR)}$ taurine modification rate, and NADH dehydrogenase 6 protein mass (5) Imaging (brain MRI) (6) Mini-Mental State Examination (MMSE) score
Evaluation items	(1) Efficacy Efficacy in this clinical trial will be evaluated with total subjects, and either subjects with L-arginine Co-Administration or no L-arginine Co-Administration. ① Primary end point: Percentage of subjects with no stroke-like episodes (100% responder rate) during the evaluation period (from 9 weeks after the start of study drug administration to the end of administration). ② Secondary end points: (i) Mitochondrial disease severity score (Japanese Mitochondrial Disease Rating Scale [JMDRS]) (ii) 50% responder rate

	(iii) Number of idiopathic focal ictal neurological signs defined in the MELAS stroke diagnostic criteria (with no consideration of confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI) (iv) Specialized tests (blood and CSF levels of taurine, lactate, and pyruvic acid and lactate/pyruvic acid ratio) (v) Imaging (brain MRI examination) (vi) Number of times intravenous L-arginine is administered both before and after administration of the study drug (vii) Number of times the patient experiences headache, nausea/vomiting, convulsions, or impaired consciousness with confirmation of high-intensity signal(s) by brain MRI (2) Safety, adverse events, and side effects
Clinical trial period	September 2013–December 2014

2. Background Information and Trial Significance

Mitochondrial myopathy, encephalopathy, lactic-acidosis, and stroke-like episodes (MELAS) is the most frequent mitochondrial disease. One base substitution in the $tRNA^{Leu(UUR)}$ gene coded by mitochondrial DNA is proposed to be the underlying cause of MELAS; however, the exact pathologic mechanism remains to be elucidated. MELAS follows an aggressive course, with recurring stroke-like episodes and damage accumulating in the central nervous system. Currently, treatment includes mitigation of cerebral infarction in acute phase of disease and improvement of energy metabolism during the chronic course of disease. However, such treatment approaches are not sufficient; therefore, the most serious clinical presentation of MELAS that needs to be

urgently addressed for the development of an effective therapeutic modality is the recurrence of stroke-like episodes. Our group was the first to discover a deficiency in anticodon taurine modification of the mutant mitochondrial $tRNA^{Leu(UUR)}$ in MELAS.[1] This taurine modification plays an important role in codon recognition for translation. We previously revealed that this taurine modification deficit led to the failure of protein synthesis in MELAS and proposed that the fundamental pathology underlying MELAS was an RNA modification disorder.[2] Furthermore, taurine supplementation to cells in culture in an *in vitro* MELAS model led to the improvement of mitochondrial function.[3] Based on these original fundamental observations, recurrent stroke-like episodes were completely suppressed for more than nine years in two patients with MELAS that were orally administered taurine.[3] Based on these results, this clinical trial will be conducted as a physician-led clinical trial of the Health, Labor, and Welfare Grant-in-Aid for Scientific Research: Overcoming Intractable Diseases Research Program (Funded by the Ministry of Health, Labor, and Welfare of Japan, H24-Nanchitou(Nan)-Ippan-068).

3. Objectives

This clinical trial will utilize taurine supplementation therapy as treatment for the suppression of recurrent stroke-like episodes in patients with the rare, incurable disease, MELAS, and examine its efficacy and safety.

4. Trial Protocol

4.1 Trial Schedule

4.1.1 Investigation Period

Case registration period: September 2013–December 2013

Investigation period: September 2013–December 2014

4.1.2 Participation Period

Period before observation: 7 days

Period of study drug administration: 52 weeks

(1) Patients who are confirmed to be eligible after informed consent is obtained will be registered.

(2) The study drug will be administered for 52 weeks, during which time the number and severity of stroke-like episodes will be determined.

4.1.3 Trial Methods

The trial will be conducted as a multicenter, open-label, phase 3 trial.

Rationale for trial design: A highly reliable, randomized, double-blind, placebo-controlled trial is not ethically possible in patients with MELAS as the average life expectancy after diagnosis is only 7.3 ± 5.0 years.[4]

4.2 Subjects

Patients who meet all of the following inclusion criteria and do not violate the exclusion criteria will be subjects of this clinical trial.

4.2.1 Inclusion Criteria

(1) Patients with a comprehensive and definitive diagnosis of MELAS who meet the Japanese

MELAS diagnostic criteria (Ministry of Health, Labour and Welfare Research Group, Koga Group, 2005) based on clinical manifestations, muscle pathology, and genetic screening.[4]

(2) Patients who have any of the following point mutations in mitochondrial DNA: A3243G, T3271C, G3244A, T3258C, or T3291C.

(3) Age, gender, and hospitalization/outpatient status will not be inquired at the time of consent.

(4) Patients who have not used L-arginine within the 78-week period before consent is obtained or those who have been using L-arginine for a minimum of 26 weeks prior to consent.

(5) Patients who meet the following criteria for stroke-like episodes* before consent is obtained:

① Patients who are not using L-arginine: at least two stroke-like episodes within the 78-week period before consent is obtained and at least one stroke-like episode within the 52-week period before consent is obtained.

② Patients who are using L-arginine and meet any of the following criteria during the period of L-arginine use:

(i) If the period of arginine use is 78 weeks or less, at least two stroke-like episodes within that period and at least one stroke-like episode within the 52-week period before consent is obtained.

(ii) If the period of L-arginine use is more than 78 weeks, at least two stroke-like episodes within the 78-week period before consent and at least one stroke-like period within the 52-week period before consent is obtained.

*A stroke-like episode for the selection criteria is defined as the presence of any of the

following abrupt-onset focal neurological deficits (with no consideration of confirmation by brain MRI):

① Hemiparesis or monoparesis

② Cortical sensory deficit (extinction)

③ Cortical sensory deficit (scintillating scotoma or cortical blindness)

④ Aphasia

⑤ Apraxia

⑥ Agnosia

(6) Patients with no history of oral taurine treatment.

(7) Patients capable of judging the clinical manifestations of a stroke-like episode.

(8) Individuals for whom informed consent for participation in this clinical trial is obtained in writing by the patients themselves before enrollment. (For minors, individuals for whom written consent is obtained from a legal guardian, and written assent is obtained from the patient themselves for participation in this clinical trial).

Rationale for inclusion criteria:

(1) In order for this trial to be comprehensive, MELAS diagnosis will be determined based on multiple parameters, such as clinical manifestations, genetic testing, and muscle pathology.

(2) As evaluation of the efficacy of the study drug on mitochondrial gene mutation rate is a planned outcome of this trial, MELAS patients with the indicated mutations will be chosen as subjects.

(3) As both males and females can be subjects, gender will not be inquired. As both

hospitalized and outpatient patients can be subjects, status will not be inquired. As stroke-like episodes occur in high frequency in both children and adults, it is possible that the efficacy of the study drug will be observed in subjects regardless of age, gender, or hospitalization/outpatient status.

(4) Patients not using L-arginine and those using L-arginine will be both chosen as subjects.

(5) This trial is designed to include patients with stoke-like episodes within the indicated time periods to allow for sufficient assessment of the efficacy of the study drug chosen.

(6) To avoid any potential confounding effects of prior taurine treatment on the outcomes of the current clinical trial, patients with a history of taurine supplementation will not be enrolled.

(7) As the primary end point is the number of stroke-like episodes, patients should to be able to recognize the clinical manifestations.

(8) As emergency measures may be necessary during a stroke, only patients whose consent is obtained before enrollment will be chosen as subjects. Furthermore, participation in this clinical trial will be decided by the free will of the patient themselves, and for minors, themselves and a legal guardian. In the event of difficulty to obtain consent from the patient, those patients for whom written consent is obtained from a legal guardian will be chosen as subjects.

4.2.2 Exclusion Criteria

(1) Patients who cannot undergo brain MRI, such as those with pacemakers.

(2) Patients with status epilepticus or those in severe coma.

(3) Patients with dementia, those who are bedridden, or those with whom communication is not possible.

(4) Patients with concomitant sepsis.

(5) Patients with severely impaired cardiac, hepatic, or renal function.

(6) Patients who require systemic administration of steroids for 2 weeks or longer.

(7) Patients who have used pyruvic acid within the 12-month period before consent is obtained.

(8) Patients who are breast feeding, pregnant, or may become pregnant.

(9) Patients with a history of hypersensitivity to the components of the study drug.

(10) Patients with a history of drug allergies.

(11) Patients who have participated in a clinical trial within the 12-month period before consent is obtained.

(12) Patients who are determined to be ineligible as subjects for other reasons by the principal investigator or sub-investigator.

Rationale for exclusion criteria:

(1) As stroke-like episodes in this clinical trial will be assessed by brain MRI, patients who cannot be evaluated by brain MRI will be excluded.

(2) Efficacy of the study drug might be impossible to determine for these patients as they cannot report symptoms due to impaired consciousness.

(3) With the progression of dementia, patients will be increasingly unlikely to report symptoms, hindering determination of efficacy. Additionally, this exclusion criterion is

included for ethical and safety reasons.

(4) Patients with concomitant sepsis will be excluded to maintain their safety.

(5) This exclusion criterion is for the safety of patients.

(6) Steroids promote vasoconstriction and reduce vascular endothelial function and can adversely impact the efficacy evaluation of the study drug.

(7) Pyruvic acid has been reported to improve the symptoms of mitochondrial disease by lowering lactate levels, which may confound the efficacy evaluation of the study drug.

(8–11) These criteria are indicated to maintain the safety of patients.

(12) This criterion is indicated to account for factors other than those indicated in (1–11) that may influence the assessment of the study drug.

4.3 Target Number of Subjects

15 subjects.

Rationale for target number of subjects: The target number of subjects are determined based on the following feasibility and statistical review-related factors:

- During the planning phase for this clinical trial, the results of three nationwide surveys focusing on neurology and pediatrics indicated that the estimated potential number of enrollees (i.e. those with two or more stroke-like episodes within the past year) were 21 subjects for the L-arginine Co-Administration and 5 subjects for the no L-arginine Co-Administration. All subjects that meet the remaining inclusion criteria, do not violate the exclusion criteria, and provide consent will be enrolled. The actual number of subjects recruited is feasible in consideration of the expected trial period.

- Taurine administered in two MELAS patients led to the complete suppression of recurrent stroke-like episodes for more than nine years.[3] Because of the small number of patients, the 100% expected responder rate from these results are conservatively estimated as 50%.
- In patients currently being treated with off-label L-arginine, the number of stroke-like episodes almost never reaches zero. Therefore, as achievement of no stroke-like episodes after the study drug administration is an objective indicator showing treatment efficacy, the 100% responder rate was adopted as the primary endpoint.
- The subjects of this clinical trial will be patients who have had at least two stroke-like episodes in the 78-week period before consent is obtained. Of those currently being treated with off-label L-arginine, those subjects with no stroke-like episodes are few and far between. Therefore, the threshold 100% responder rate is estimated as 5%.
- For a hypothesis of a threshold 100% responder rate of 5% and an expected 100% responder rate of 50% when 15 subjects are integrated, we can ensure a power of 90% or above with a 5% two-sided significance. Furthermore, we can ensure a power of 80% or more with ten subjects in the no L-arginine Co-Administration and five patients in the L-arginine Co-Administration.
- Efficacy in this clinical trial will be evaluated with the total cases. Further evaluation will be performed with no L-arginine Co-Administration and L-arginine Co-Administration subjects separately.

5. The Study Drug

5.1 The Study Drug

Study drug ID: KN01

Generic name: Taurine

Ingredients and dosage form: 1 g of taurine in 1.02 g, powder

Dosage and administration method: The total daily dose of the study drug, determined by patient body weight categories indicated below, will be administered orally three times daily after meals.

Weight*	Amount per Day
40 kg or more	12 g
25–39 kg	9 g
15–24 kg	6 g
Less than 15 kg	3 g

*Body weight before the observation period

5.2 Handling of the Study Drug

The study drug will be issued once the provision of the study drug is agreed upon between the coordinating investigator and the study drug provider. The study drug manager will assure the storage and management of the study drug in accordance with the procedural manual for administration of the study drug that is created by those participating in the trial independently. Upon completion of the trial, the coordinating investigator will recover any unused drug and packaging. The study drug shall not be used for any purpose other than this clinical trial.

6. Dosage and Administration

6.1 Dosage and Administration Method

The daily amount of the study drug, determined by patient body weight categories indicated

below, will be administered orally three times daily after meals.

Weight*	Amount per Day
40 kg or more	12 g
25–39 kg	9 g
15–24 kg	6 g
Less than 15 kg	3 g

*Body weight before the observation period

Rationale for dosage and administration:

In this clinical trial, the taurine dose will be 12 g per day divided into three doses, which is higher than the dose for the currently approved indications for taurine, hyperbilirubinemia, and congestive heart failure, which is 3 g per day divided into three doses. The decision to exceed the previously approved dosage is based on the following factors indicating that 12 g per day (divided into three doses) is the highest taurine dose that is possible to confirm as safe with potential efficacy.

(1) In a single-dose toxicity test (rabbit, intravenous administration) and repeated dose toxicity/reproductive and developmental toxicity test (rat, oral administration), the no-observed-adverse-event level was 1,000 mg/kg or more.

(2) As a mouse model of MELAS does not exist,[5] we cannot assess the potential deficit improvements with taurine treatment in a model mouse as a preclinical study; thus, we must refer to previous clinical studies.

(3) The safety and efficacy of 12 g of taurine per day was confirmed in patients with hyperbilirubinemia.[6]

(4) No serious adverse events or side effects were reported in two previous reports of off-label use of taurine.

① One study reported safe oral administration of 6 g/day taurine three times daily for 6 months in 12 patients with muscle cramps resulting from non-alcoholic cirrhosis.[7]

② One study reported safe oral administration of 6 g/day taurine three times daily (taken after each meal) for 14 days in five patients with essential tremor for more than 15 years.[8]

(5) A previous study on taurine treatment in patients with MELAS confirmed the safety and efficacy of 12 g/day taurine divided into three doses.[3]

(6) In two patients with MELAS who are currently undergoing continuous treatment with taurine, the safety and efficacy of the administration method and dosage to be used in this clinical trial, 12 g per day (divided into three doses) has been confirmed.

(7) In pediatric patients, although taurine supplementation was administered for other indications, in a study of 33 individuals with ages ranging from infancy to the age of 16 years, subjects were administered between 0.5 g and 6 g taurine per day. Among a total of 28 cases with information on side effects, no taurine-associated side effects were observed.

6.2 Administration Period

The administration period will be 52 weeks.

Rationale for administration period:

Based on previous research on taurine treatment in MELAS and the status of MELAS patients currently undergoing continuous administration, an administration period of 52 weeks is determined sufficient for adequate assessment of its efficacy.

6.3 Allowed and Disallowed Concomitant Treatments and Drugs

6.3.1 Disallowed Concomitant Drugs

1) Pyruvic acid

2) Oral L-arginine (patients who are not taking oral L-arginine at the start of the clinical trial)

Rationale:

(1) Oral L-arginine is disallowed based on studies demonstrating its vasodilatory effect and efficacy in stroke prevention, which may confound the accurate assessment of the efficacy of the study drug. There is a risk that it may augment or hinder the effect of the study drug.

(2) Oral L-arginine is disallowed after the start of the clinical trial because of the potential impact on the assessment of the efficacy of the study drug.

6.3.2 Disallowed Concomitant Treatments

Steroid treatments:

Systemic administration of steroids for 2 weeks or longer is prohibited.

Rationale:

As steroids promote vasoconstriction and reduce vascular endothelial function, concomitant use of steroids can adversely impact the efficacy evaluation of the study drug.

6.3.3 Allowed Concomitant Drugs and Treatments

Medication that the principal investigator or sub-investigator determine to be necessary may be used. However, the medication name, dosage and administration, administration

period, and reason for concomitance will be described in the case report.

・Emergency treatment drugs:

No limit (includes intravenous L-arginine)

・Drugs that can be used during the trial period, limiting changes to the dose or administration as much as possible:

Nitric acid, vasodilators with nitric oxide inducers, coenzyme Q, anti-epileptic drugs (if taken continuously since the pretrial period), and oral L-arginine (if taken for 26 weeks or more before consent is obtained).

Rationale

For drugs used in emergencies, especially in the status epilepticus, lifesaving treatment must be the priority, and limiting their use is difficult. Consequently, the use of emergency treatment drugs will not be limited, and the use of intravenous L-arginine will be allowed. Nitric acid, vasodilators with nitric oxide inducers, coenzyme Q, and antiepileptic drugs are medications conventionally used for MELAS prevention. As their discontinuation would be problematic, their use is permitted as long as significant changes in their dosage and administration are avoided, if possible. For orally administered L-arginine, its use is permitted for patients who have been using it for at least 26 weeks before the beginning of the study drug administration and will continue using it after the beginning of the trial. Any changes to the dosage and administration method of L-arginine in these patients will be limited if possible, to control its effects on the determination of efficacy for the study drug.

7. Observations, Evaluation Items, and Time Period

7.1 Observation and Examination Schedule

Observations and examinations will be conducted in accordance with the following schedule.

Table 1. Observation/Examination/Evaluation Schedule

		Consent	Period Before Observation		Observation Period						Discontinuation
			-1 week		0 week		4 weeks	12 weeks	24 weeks	36 weeks	52 weeks	
Day			-7～0		0		28	84	168	252	364	
Acceptable Range (Days)							± 7	± 7	± 14	± 14	± 14	
Consent Obtained		●										
Patient Background Survey[1]			●									
Brain MRI			●[2]			●[3]					●	●
Registration				●								
Observation of Number of Stroke-Like Episodes						●[4]						●[4]
MELAS Severity[5] (12-Lead echocardiogram [ECG])					●						●	●
Physical Examination[6]					●		●	●	●	●	●	●
In Hospital Blood Testing[7]	Hematological Tests				●		●	●	●	●	●	●
	Biochemical Tests				●		●	●	●	●	●	●
Specialized Testing	Blood Tests[8]				◎		◎				◎	◎
	CSF Tests[9]				◎						◎	◎
	Blood Leukocyte Tests[9]				◎						◎	◎
MMSE Score					●						●	●
Study Drug Prescription						●	●	●	●	●		
Study Drug Compliance Check						●	●	●	●	●	●	●
Adverse Events Check						●	●	●	●	●	●	●
Co-Administered[10]		●	●	●	●	●	●	●	●	●	●	●

● Hospital implementation/measurement item, ◎: Centralized facility measurement item

1) The following items will be examined:

① Patient gender, birth date, and age;

② Number of stroke-like episodes in the past 78-week period (and L-arginine co-administration period for the L-arginine co-administration);

③ Mitochondrial DNA mutation points (A3243G, T3271C, G3244A, T3258C, T3291C);

④ Blood pressure, pulse, height, and weight;

⑤ Complications and smoking history;

⑥ Medical history of the 78-week period before consent is obtained.

2) Brain MRI scans obtained within the 4-week period before the start of study drug administration can be used.

3) Brain MRI scans will be obtained when stroke-like episodes occur.

4) The occurrence of the stroke-like episodes will be confirmed. The stroke-like episode will be determined in accordance with the MELAS stroke

diagnostic criteria: Fulfillment of both ① and ②:

① Any of the following abrupt-onset focal neurological deficits:

(1) Hemiparesis or monoparesis

(2) Cortical sensory impairment (elimination of sensation)

(3) Cortical sensory impairment (scintillating scotoma or cortical blindness)

(4) Aphasia

(5) Apraxia

(6) Agnosia

② Confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI.

5) MELAS severity will be determined in accordance with the Japanese mitochondrial disease rating scale (JMDRS).

6) Weight, temperature, blood pressure, and pulse while sitting at rest.

7) Hematology: red blood cell count, leukocyte count, platelet count, hemoglobin level, hematocrit level, and hemogram.

Biochemical Examination: total protein, albumin, glucose, hemoglobin A_1c (HbA_1c) value, aspartate transaminase (AST, GOT), alanine transaminase (ALT, GPT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (γ-GTP), creatine kinase (CK), total bilirubin (T-Bil), direct bilirubin (D-Bil), blood urea nitrogen (BUN), creatinine (Cre), uric acid, triglycerides (TG), total cholesterol (T-Cho), Na, K, Cl.

8) Blood test: blood lactate (deproteinized), blood pyruvic acid (deproteinized), and blood amino acid analysis (39 types) will be measured with SRL.

Cerebrospinal fluid (CSF) examination: CSF lactate (deproteinized), CSF pyruvic acid (deproteinized), and CSF amino acid analysis (39 types) will measured with SRL.

Blood leukocyte examination: mitochondrial gene mutation rate, $tRNA^{Leu(UUR)}$ taurine modification rate, and NADH dehydrogenase 6 protein mass will be measured at the Kawasaki Medical School/Japan Medical Institute for the Elderly.

9) Optional

10) Information, co-administration period, and reason for co-administration for drugs and treatments used since the 4-week period before consent until the end of the observational period will be surveyed.

7.1.1 Observation of Stroke-Like Episodes and their Severity

(1) Observation of Stroke-Like Episodes

Stroke-like episodes will be determined based on the following MELAS stroke diagnostic criteria

Table 2. MELAS stroke diagnostic criteria: Fulfillment of both ① and ②

① Any of the following abrupt-onset focal neurological deficits:

(1) Hemiparesis or monoparesis

(2) Cortical sensory deficit (extinction)

(3) Cortical sensory deficit (scintillating scotoma or cortical blindness)

(4) Aphasia

(5) Apraxia

(6) Agnosia

② Confirmation of high-intensity signal(s) with diffusion-weighted brain MRI.

It should be noted that if a new lesion is found by brain MRI even in the presence of multiple abrupt-onset focal neurological deficits, if the lesion is confirmed by brain MRI within 2 weeks of the signs, they will be counted as one episode. Additionally, if the lesion appears within 2 weeks of a previous stroke-like episode, a lesion confirmed by brain MRI will be considered as part of the same episode.

In addition to the abrupt-onset focal neurological deficits measured by the MELAS stroke diagnostic criteria, the presence of the following symptoms will be recorded:

(1) Headache

(2) Nausea and vomiting

(3) Convulsions

(4) Impaired consciousness

(2) MELAS Degree of Severity

Prior to the start of the study drug administration and at the time of discontinuation after 52 weeks of treatment, the MELAS degree of severity will be determined in accordance with the Japanese mitochondrial disease rating scale (JMDRS; Ministry of Health, Labour and Welfare Research Group, Koga Group, 2005) that is adopted with modifications from the European Neuromuscular Conference (ENMC) mitochondrial disease rating scale (2003).

Note that, at the time of evaluation of subjects for MELAS degree of severity, 12-lead electrocardiography and echocardiography (ejection fraction [EF], left ventricular diastolic dimension [LVDD], left ventricular systolic dimension [LVSD], LVSD, pulse wave Doppler [PWD], tricuspid regurgitation peak gradient [TRPG], asynergy, and valve) will be conducted. The estimated glomerular filtration rate (eGFR) will be calculated based on the following formula:

$$eGFR\ (mL/min/1.73\ m^2) = 194 \times Cr^{-1.094} \times age^{-0.287}\ (male)$$

$$eGFR\ (mL/min/1.73\ m^2) = 194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739\ (female).$$

7.1.2 Physical Examination

The following measurements will be taken prior to the start and after 4, 12, 24, 36, and 52 weeks (at the time of discontinuation) of the study drug administration:

(1) body weight

(2) body temperature

(3) blood pressure and pulse (at rest while sitting)

7.1.3 In-Hospital Blood Tests

These tests will be performed prior to the start and after 4, 12, 24, 36, and 52 weeks (at the time of discontinuation) of the study drug administration. A specific time of day for blood collection is not specified. However, the amount of time that has elapsed since the previous meal and the time of previous administration of the study drug will be recorded.

Hematological tests: red blood cell count, leukocyte count, platelet count, hemoglobin level, hematocrit level, and hemogram.

Biochemical Examinations: total protein, albumin, glucose, hemoglobin A_1c (HbA_1c), aspartate transaminase (AST, GOT), alanine transaminase (ALT, GPT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (γ-GTP), creatine kinase (CK), total bilirubin (T-Bil), direct bilirubin (D-Bil), blood urea nitrogen (BUN), creatinine (Cre), uric acid, triglycerides (TG), total cholesterol (T-Cho), Na, K, Cl.

7.1.4 Specialized Tests

These evaluations will be conducted at a centralized facility. A specific time of day for blood

and CSF collection is not specified. However, the amount of time that has elapsed since the previous meal and the time of previous administration of the study drug will be recorded.

(1) SRL Measurement (by SRL Medisearch Inc., Tokyo, Japan)

Prior to the start and after 4 and 52 weeks (at the time of discontinuation) of the study drug administration:

Blood tests: blood lactate (deproteinized), blood pyruvic acid (deproteinized), and blood amino acid analysis (39 types).

Prior to the start and after 52 weeks (at the time of discontinuation) of the study drug administration:

CSF examination (optional): CSF lactate (deproteinized), CSF pyruvic acid (deproteinized), and CSF amino acid analysis (39 types).

(2) Measurements at Kawasaki Medical School/Japan Medical School for the Elderly

Prior to the start and after 52 weeks (at the time of discontinuation) of the study drug administration:

Peripheral blood leukocyte examination (optional): mitochondrial gene mutation rate, mitochondrial $tRNA^{Leu(UUR)}$ taurine modification rate, and NADH dehydrogenase 6 protein mass.

7.1.5 Imaging

Prior to the start and after 52 weeks of the study drug administration (at the time of discontinuation) and in the presence of a stroke-like episode defined by the MELAS stroke diagnostic criteria ①, brain MRI will be conducted. The imaging method will be as

follows: diffusion-weighted image (axial), magnetic resonance angiography (MRA) image (intracranial), fluid-attenuated inversion recovery (FLAIR) image (axial), T2-weighted image (axial), T1-weighted image (axial), and T2*-weighted image (axial). Additionally, if possible, an apparent diffusion coefficient (ADC) map will be calculated. MRI scans accompanying stroke-like episodes will be conducted as quickly as possible, but it is essential that they are performed within 2 weeks after the occurrence of the event at most.

7.1.6 MMSE Score

MMSE scores will be determined prior to the start and after 52 weeks (at the time of discontinuation) of the study drug administration.

7.2 Patient Characteristics

The following items will be determined prior to the start of the study drug administration:

(1) Patient gender, birth date, and age

(2) Items related to the stroke-like episodes that occurred within the 78-week period before consent is obtained:

① Number

② Length

③ Diagnostic results of brain MRI studies (only if one was conducted)

④ Status of intravenous L-arginine use

(3) Brain MRI findings (brain MRIs obtained within the 4-week period before the start of

study drug administration are acceptable)

(4) Mitochondrial DNA point mutations (A3243G, T3271C, G3244A, T3258C, T3291C)

(5) Blood pressure, pulse, height, and weight

(6) Complications, smoking history

(7) Medical history for the 78-week period* before consent is obtained.

*For patients continuing the use of oral L-arginine, the period of oral L-arginine use (26 weeks or more, up to 78 weeks)

7.3 Determination of Efficacy Endpoints

7.3.1 Primary Endpoint for Efficacy (100% responder rate)

The primary endpoint is the percentage of cases with no stroke-like episodes (100% responders) during the evaluation period (between 9 weeks after the start of study drug administration and the time of its discontinuation).

Rationale for 100% responder rate as the primary endpoint:
In patients currently being treated with off-label L-arginine, the number of stroke-like episodes almost never reaches zero. Therefore, as achievement of no stroke-like episodes after the study drug administration is an objective indicator showing treatment efficacy, the 100% responder rate was adopted as the primary endpoint.

Stroke-like episode diagnosis method

Stroke-like episodes will be diagnosed based on the MELAS stroke diagnostic criteria defined below.

Table 3. MELAS stroke diagnostic criteria: Fulfillment of both

① and ②
① Any of the following idiopathic focal ictal neurological signs:
1) Hemiparesis or monoparesis
2) Cortical sensory deficit (extinction)
3) Cortical sensory deficit (scintillating scotoma, cortical blindness)
4) Aphasia
5) Apraxia
6) Agnosia
② Confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI.

It should be noted that a new lesion found by brain MRI even in the presence of multiple abrupt-onset focal neurological deficits, if the lesion is confirmed by brain MRI within 2 weeks of the signs, will be counted as one episode. Additionally, if the lesion appears within 2 weeks of a previous stroke-like episode, a lesion confirmed by brain MRI will be considered part of the same episode.

Stroke-like episode evaluation period

(1) Subjects for no L-arginine Co-Administration:

Stroke-like episodes will be compared between the following:

Before the start of the trial: the 78-week period before consent is obtained

and

After the start of the trial: the period between 9 weeks after the start of the study drug administration and the end of administration (first 8 weeks after the start of the study drug administration will not be included in the evaluation period).

(2) Subjects for L-arginine Co-Administration:

Stroke-like episodes will be compared between:

Before the start of the trial: the period of L-arginine treatment before consent is obtained (26 weeks or more, up to 78 weeks)

and

After the start of the trial: the period between 9 weeks after the start of the study drug administration and the end of administration (first 8 weeks after the start of the study drug administration will not be included in the evaluation period).

Rationale for the diagnosis of stroke-like episodes in this trial:

As there are no diagnostic criteria for MELAS stroke-like episodes in adults, the new MELAS stroke diagnostic criteria are established in this study. There is a stroke scale for pediatric patients with MELAS (Ministry of Health, Labor, and Welfare Research Group, Koga Group, 2005); however, as it includes items such as headache, nausea/vomiting, convulsions, and impaired consciousness that can result from etiologies other than stroke, it is excluded from the diagnostic criteria. As the present diagnostic criteria are specifically

aimed at distinguishing items with a causal relationship to stroke, a stroke-like episode is established as the presence of idiopathic focal neurological signs and confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI.

Rationale for the evaluation period for stroke-like episodes in this trial:

(1) Subjects for no L-arginine Co-Administration:

The evaluation period before the administration of the study drug is set as the maximum period possible for evaluation, the 78-week period before consent is obtained. The evaluation period after administration of the study starts at 9 weeks after the start of the study drug administration; the first 8 weeks are excluded from evaluation, as the effects of the study drug are not expected to manifest for a period of time at the beginning of its administration.

(2) Subjects for L-arginine Co-Administration:

The evaluation period before the administration of the study drug is set to 78 weeks before consent is obtained. As the period of L-arginine use is not expected to be consistent across subjects, to standardize the L-arginine Co-Administration in this clinical trial, the period of L-arginine use is required to be a minimum of 26 weeks before consent is obtained, and this period is set as the evaluation period before the administration of the study drug. L-arginine dose modification during this period is acceptable.

The evaluation period after the start of the study drug administration is the same as that for the no L-arginine Co-Administration. As a general rule, the L-arginine dose is not changed after the start of the study drug administration.

7.3.2 Secondary Endpoints for Efficacy

(1) Improvement of clinical symptoms

Clinical symptoms will be evaluated according to the JMDRS criteria (Ministry of Health, Labor, and Welfare Research Group, Koga Group, 2005; Appendix 2)

(2) 50% responder rate

The percentage of cases with 50% or more reduction in stroke-like episodes for each 4 weeks of the evaluation period after the start of study drug administration, in comparison with the number of stroke-like episodes before its administration.

(3) Number of abrupt-onset focal neurological deficits defined by the MELAS stroke diagnostic criteria (with no consideration of confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI).

(4) Specialized testing (blood/CSF taurine, lactate, and pyruvic acid levels, and lactate/pyruvic acid ratio)

(5) Imaging studies (brain MRI scans)

(6) Number of times intravenous L-arginine is used before and after the start of study drug administration.

(7) Number of times high-intensity lesion(s) are confirmed with diffusion-weighted brain MRI in the presence of headache, nausea/vomiting, convulsions, or impaired consciousness.

Rationale for secondary endpoints in this clinical trial:

(1) A previous study[3] showed that clinical symptoms improved after taurine treatment.

(2) The percentage of subjects with 50% reduction in the number of stroke-like episodes is chosen as a clinically significant endpoint.

(3) Only abrupt-onset focal neurological deficits are chosen, and confirmation by the presence of high-intensity lesion(s) with diffusion-weighted brain MRI will not be necessary.

(4) In a previous study,[3] blood/CSF taurine, lactate, and pyruvic acid levels, and lactate/pyruvic acid ratio decreased after taurine treatment.

(5) In a previous study,[3] abnormal signals that reflect stroke-like episodes by brain MRI disappeared after taurine treatment.

(6) Changes in the status of intravenous L-arginine use will be assessed, as its use as emergency treatment for stroke-like episodes is expected.

(7) MRI findings will be assessed for symptoms other than the neurological symptoms defined by the MELAS stroke diagnostic criteria.

7.4 Safety Evaluation Items

7.4.1 Evaluation Items

(1) Subjective symptoms/objective findings (including worsening of complications)

(2) Physical examination

(3) Clinical examination

7.4.2 Handling of Vital Signs and Laboratory Test Values

If the vital signs and clinical laboratory values deviate from the standard, the abnormal values will be recorded in the case report. The clinical examination items will use the standards of measurement used by each institution for each item, and the standard values from the following “Vital Signs Standard Values” chart will be used for vital signs.

<Vital Signs Standard Values>

Blood Pressure (mmHg)	Systolic Blood Pressure Standard Value: 90–140
	Diastolic Blood Pressure Standard Value: 50–90
Pulse (beats per minute)	Standard Value: 50–110
Temperature (°C)	Standard Value: 35–37°C

Values recorded after the start of the study drug administration will be compared to those recorded before the start of the study drug administration to determine if there are any

abnormal variations in each measurement. The range of physiological variation in each patient and its clinical significance will be considered based on this determination. In this case, regardless of the presence of a change from a normal value to an abnormal value or from an abnormal value to worsening of an abnormal value, if abnormal variation is deemed not present, the reason for this decision will be recorded in the medical record. Additionally, if there is an item with a missing value at the beginning of the study drug administration, if every subsequent value is within the abnormal range, this item will be treated as an abnormal variation.

The degree of abnormal variation (severity) will be determined with reference to the 80th issue of the Ministry of Health and Welfare Pharmaceutical Affairs Bureau Division Notification on Pharmaceuticals, "Severity classification criteria for side effects of pharmaceuticals, etc." However, the definitions for group 1, group 2, and group 3 defined in the 80th issue will correspond to the definitions of mild, moderate, and severe, respectively, in this trial.

When abnormal variation is found, it will be treated as an adverse event and follow-up will be performed if necessary. However, even when abnormal variation is not found, items determined to be adverse events by either the principal investigator or sub-investigator will be treated as adverse events, and follow-up will be performed if necessary. Follow up will be conducted in accordance with the procedures defined in section 7.4.3 "Follow-Up."

If the principal investigator or sub-investigator determines the adverse event to be causally related to the study drug—in reference to the causal relationship criteria defined in Section 9.2 "Dealing with Adverse Events"—it will be recorded in the case report. The range of physiological variation for each examination item and combined treatments, etc. will be considered in the decision-making. If the study drug is determined not to be causally

related to abnormal variations, the rationale will be recorded in the case report.

In addition to the abovementioned steps, evaluation items that are not measured but are determined to be adverse events by the principal investigator or sub-investigator will be treated as adverse events.

7.4.3 Follow-Up

If adverse events or clinically significant abnormalities in examination values are found, if the subject becomes pregnant, or if abnormalities are found in subjective symptoms/objective findings, the principal investigator or sub-investigator will perform the appropriate examination or inspection, even after the completion or discontinuation of the trial, to assure the safety of the subject.

Follow-up is carried out, as a general rule, even if the subjects recover from the adverse event or return to their status before administration. The examination items on the day of occurrence (the day abnormal variations in examination items are found), degree (severity), study drug administration status, any intervention performed to alleviate the adverse event (excluding changes in dosage or discontinuation of treatment with the study drug), outcome (day of the resolution of the adverse event), and the degree of causal relationship with the study drug (four stages) will be recorded in the case report. Furthermore, decision rationale, treatment details, elapsed time, other comments, among others, will be recorded in detail in the medical record. For clinical test items not specified in the trial protocol, in addition to the abovementioned details, measurement values at the time of assessment and/or any alternative data will be recorded.

If there are adverse events, follow-up will be conducted until their resolution or until the

outcome is clear, and the laboratory test values with abnormal variations will be measured until the values stabilize.

7.5 Other Evaluation Items

- Hemoglobin A_1c value
- Mitochondrial gene mutation rate of blood leukocytes, $tRNA^{Leu(UUR)}$ taurine modification rate, and NADH dehydrogenase 6 protein mass
- MMSE score

7.6 Concomitant Drugs and Treatments

From 4 weeks before consent is obtained until the end of the observation period or until discontinuation, details, concomitance period, and reason for concomitance will be surveyed and recorded in the case report for all drugs and treatments in use. For L-arginine, the dose of oral L-arginine used before consent is obtained (26 weeks or more, up to 78 weeks) will also be recorded.

8. Obtaining Informed Consent and Providing Information to Subjects

8.1 Procedures for Obtaining Informed Consent

The principal investigator will create explanatory documents and a consent form (hereafter, called consent/explanatory documents) as well as explanatory documents for underage patients and an assent document (hereafter called assent/explanatory documents). Consent/explanatory documents and assent/explanatory documents will be put into one integrated and complete document, which will be revised if necessary. This document will be

submitted at length to the medical institution(s) where the trial will be conducted, and approval from the institutional review board (IRB) will be received before the clinical trial begins.

Before subjects participate in the trial, the principal (sub) investigator will fully explain the details using the consent/explanatory documents and—after confirming that the subjects satisfactorily understand—consent for participation will be obtained in writing.

In cases where subjects are underage or obtaining consent from the subjects themselves is difficult, consent will be obtained from a legal guardian. Even in these cases, details will be fully explained using the consent/explanatory documents, and consent for participation in the clinical trial will be obtained in writing. In this event, records relating to consent and the relationship between the legal guardian and the subject will be recorded. Additionally, if subjects recover to a state where giving consent is possible during the trial, the principal (sub) investigator will once again conduct an explanation of consent and obtain written consent from the subjects themselves.

For underage subjects who are middle school-aged and older, assent will be obtained in writing. For underage subjects over the age of seven who are not yet in middle school, obtaining assent in writing will be attempted as appropriate. However, in cases where a signature cannot be obtained from the subject or in cases where assent is obtained orally but not in writing, a legal guardian will sign the consent form, and it will be noted in the records that assent is acquired from the subject. Legal guardians are always required to provide written consent after assent is obtained from the subject.

8.2 Matters Explained for Consent

The principal (sub) investigator will explain the details of the clinical trial to subjects and/or legal guardians using explanatory documents that include the following matters:

(1) The clinical trial is in accordance with research.

(2) The objective of the clinical trial.

(3) The name, title, and contact information of the principal and sub investigators.

(4) The method for the clinical trial (the trial's testing aspects and subject selection criteria).

(5) The expected clinical benefits as well as risks and inconveniences.

(6) If a patient becomes a subject, other treatment methods available for that subject and the expected significant risks and benefits.

(7) The expected length of participation of the subject in the clinical trial.

(8) The subject's participation in the trial is voluntary, and the subject or their legal guardian can refuse or withdraw the subject from the trial at any time. In addition, the subject will not be treated unfavorably because of refusal/withdrawal and will not lose benefits that they should have received because they did not participate.

(9) Monitors, auditors, IRB, among others, as well as the regulatory authorities will be able to view the original documents pertaining to medical care. At that time, subject privacy will be protected. Additionally, subjects and/or legal guardians will be allowed to view the documents with their seal or signature on the consent form.

(10) Subject privacy will be protected even in the event that the clinical trial results are published.

(11) Consultation services at the medical institution where the trial will be implemented that should be referenced to or contacted if subjects wish to obtain further information relating

to subject and clinical trial rights or if adverse health events related to the clinical trial occur.

(12) Compensation and treatment that can be provided to the subject if adverse health events related to the clinical trial develop.

(13) The type of IRB that will examine and discuss the appropriateness of this clinical trial, and matters that will be discussed specifically for this study that are not examined and discussed by all IRBs.

(14) The expected number of subjects participating in the trial.

(15) If information that can possibly influence the intention of the subject or their legal guardian to continue participating in the trial is obtained, it will be promptly conveyed to the subject or their legal guardian.

(16) Conditions and reasons for the discontinuation of participation in the trial.

(17) Details in the event that a cost to subjects is necessary.

(18) Details in the event that compensation (e.g., monetary payment) is made to the subject (arrangements for payment calculation).

(19) Conditions subjects must abide by.

8.3 Management of Consent/Explanatory Documents

After the investigator who explains the details signs or seals and dates the consent and/or assent form, a copy of this, along with the explanatory documents, will be hand-delivered to the subject/legal guardian, and the originals will be affixed to the medical records. When personnel collaborating with the trial provide supplementary explanations, that individual's seal or signature and the date will be recorded. Additionally, in the case of electronic charts,

after the documents are incorporated electronically, the originals will be stored. For subjects for whom informed consent is obtained, the principal investigator will record the date on which consent is obtained, such as the subject code, and create a “subject identification code list.”

8.4 Communication of Information and Revisions to Informed Consent and Explanatory Documents

In the event that new information is obtained that can possibly influence the intention of the subject or their legal guardian to continue participating in the trial, the principal (sub) investigator will convey that information promptly to the subject/legal guardian, confirm whether the subject/legal guardian intends for the subject to continue participation in the clinical trial, and record that information.

Additionally, if consent/explanatory documents and assent/explanatory documents are modified based on that information and approval from the IRB of each medical institution, the principal (sub) investigator will once again provide an explanation using the modified consent/explanatory documents and/or assent/explanatory documents for the already participating subject and/or their legal guardian and, depending on whether they intend to continue participation, obtain written consent/assent (particulars are the same as those for obtaining consent for the first time).

9. Ensuring Subject Safety

9.1 Basics

Throughout the participation of subjects in the trial, the principal (sub) investigator will

conduct necessary and appropriate observations and examinations to ensure subject safety. In case of adverse events, appropriate measures will be taken as necessary, and the cause will be investigated with attention to insurance of patient safety.

9.2 Dealing with Adverse Events

9.2.1 Definition of Adverse Events

Adverse events are any unfavorable medical events (including abnormal laboratory test values) occurring with the administration of the study drug, with no regard to their potential causal relationship with the administration of the study drug. Adverse events occurring until 28 days after the completion of the study drug administration will be included.

However, the following events and abnormal laboratory values, considered to be due to an underlying disease, will not be treated as adverse events.

[Events]

- Stroke-like episodes
- Status epilepticus
- Muscle weakness, fatigability, ataxia, sensorineural hearing loss, myoclonus, hypertrophic cardiomyopathy, heart block, and exacerbation of diabetes mellitus

Additionally, in the event that an adverse event occurs, follow-up will be conducted until that subject has recovered or returned to their state before the administration of the study drug. When subjects have either recovered or recovered with after-effects as a result of adverse events—in cases other than death—the reason will be noted in the medical chart when follow-up is determined to be no longer necessary.

9.2.2 Identifying Adverse Events

For all adverse events, the principal (sub) investigator will identify and record the day of appearance, day of disappearance, degree of severity (serious/not serious), presence or absence of treatment, outcome, action taken with the study drug, and causal relationship with the study drug in the case report.

9.2.3 Definition and Reporting of Serious Adverse Events

Serious adverse events are the adverse events listed below:

(1) Death

(2) Events that may lead to death

(3) Admission to a hospital or clinic for treatment, or extension of hospitalization (hospitalizations for examinations excluded)

(4) Impairment

(5) Events that may lead to impairment

(6) Serious conditions resulting from (1) to (5)

(7) Congenital diseases or abnormalities in future generations

When a serious adverse event appears, the principal (sub) investigator will fill in the necessary items of the “Serious Adverse Event Report” and report directly to the head of the medical institution where the trial is being conducted. They will also inform the coordinating investigator and the study drug provider of the appearance of the serious adverse event. The coordinating investigator will confirm the details of the adverse event report—received from

the principal investigator—and notify the principal investigators at other participating medical facilities of that adverse event report.

Procedures for managing safety reports will be created separately in accordance with the "Safety Report Management Procedures."

9.2.4 Causal Relationship with the Study Drug

Causal relationships with the study drug will be identified in accordance with the criteria in the table below.

Table 4. Causal Relationship Identification Criteria

Classification	Criteria
1. Clearly related	When there is an obvious temporal correlation (including the course after administration is discontinued), and the situation corresponds to any of the following: if the same findings are coincident with additional administration, a positive result on drug sensitivity testing (e.g. lymphocyte culture, skin test), or a toxic level of the study drug in bodily fluids (e.g. blood).
2. Probably related	When there is an obvious temporal correlation (including the course after administration is discontinued), and factors other than the study drug, such as underlying disease, complications, concomitant drugs, and concomitant treatments, can, for the most part, be ruled out.

3. The absence of relationship cannot be conclusively established	When there is an obvious temporal correlation (including the course after administration is discontinued), and other factors such as underlying disease, complications, concomitant drugs, and concomitant treatments can, for the most part, be ruled out. However, the possibility that the adverse event results from the study drug cannot be excluded (for example, events where there are reports of the same event in the past for analogous compounds, events inferred from pharmacological action)
4. No relation	When there is no temporal correlation or the event can be clearly explained as due to other factors such as an underlying disease, complications, concomitant drugs, or concomitant treatments.

9.2.5 Extent of Adverse Events (Severity)

The extent of adverse events will be identified in accordance with the criteria in the table below.

Table 5. Adverse Event Severity Identification Criteria

	Criteria
1. Mild	To the extent that adverse event(s) do not affect the subject's daily life. The subject is able to continue administration of the study drug without treatment for associated symptoms or any change to the study drug dosage, etc.

2. Moderate	To the extent that the adverse even(s) cause some impediment to the subject's daily life. The subject requires treatment for associated symptoms, or changes in dose, suspension, or discontinuation of the study drug (excluding discontinuation due to patient request).
3. Severe	To the extent that the tasks of daily life are impossible for the subject. There is no choice but to provide treatment for adverse event(s), in addition to discontinuation of administration of the study drug (excluding discontinuation due to patient request).

9.2.6 Definition of Side Effects

Adverse events for which a causal relationship with the study drug cannot be denied (1. Clearly related, 2. Probably related, and 3. The absence of relationship cannot be conclusively established) will be treated as side effects.

Unpredictable side effects are those that are not recorded in the study drug overview documents, or those for which, though they are recorded, the nature and severity do not conform to the recorded contents.

9.3 Expected Side Effects of the Study Drug

The expected side effects of the study drug are as follows (based on the pharmaceutical product insert provided for 98% Taurine "Taisho" [2007]):

Thirty-eight incidences of side effects were seen in 30 (2.82%) of a total of 1,064 cases. The main side effects for the digestive system were as follows: nausea in 5 (0.47%), diarrhea in 4 (0.38%), abdominal discomfort in 4 (0.38%), constipation in 3 (0.28%), loose stools in 3 (0.28%), loss of appetite in 3 (0.28%), exacerbation of peptic ulcer in 1 (0.09%), and

unspecified in 5 (0.47%) cases. Other side effects were hypersensitivity (4 cases with rash, 0.38%), full body symptoms (2 cases with fatigue, 0.19%; 1 case with fever incident, 0.09%), neuropsychiatric alterations (1 case with drowsiness, 0.09%; 1 case with euphoria, 0.09%), and central nervous system alterations (1 case with headache, 0.09%) [at the end of reevaluation].

10. Discontinuation Criteria and Procedures for Each Subject

10.1 Discontinuation Criteria

The trial will be discontinued in following conditions: (If the trial is discontinued, the reason will be determined and recorded in the case report; additionally, the specified examinations will be implemented to the fullest extent possible at the time of discontinuation.)

(1) If the subject or legal guardian withdraws consent.

(2) If the subject or legal guardian requests a change or discontinuation of treatment.

(3) If the principal (sub) investigator determines that continuation in the trial is inappropriate because of adverse events (e.g., worsening of complications or diagnosis of a new disease).

(4) If the principal (sub) investigator determines that continuation in the trial is not reasonable because of a worsening of the underlying disease.

(5) If the subject’s place of residence changes, etc. and the subject is no longer able to visit the predetermined hospital.

(6) If the subject becomes pregnant.

(7) If the subject is found to be incompatible with the selection criteria or to violate the

exclusion criteria.

(8) If a serious deviation from the clinical trial protocol is found.

(9) If the principal (sub) investigator determines that continuation in the trial is not appropriate for other reasons.

10.2 Discontinuation Procedures

If the trial is discontinued because of a safety issue, such as adverse events or worsening of the underlying disease/complications, the principal (sub) investigator will promptly take appropriate action, conduct the necessary examinations to the full extent as possible after discontinuation, and record parameters such as the day of discontinuation, reason and circumstances that led to the discontinuation, and the treatment implemented in the case report. Additionally, the progression will be observed until follow-up is determined to be no longer necessary.

11. Statistical Analysis

11.1 Statistical Considerations

The main statistical items for this clinical trial are detailed in the following sections. (Details will be separately included in the “Statistical Analysis Protocol.”)

11.2 Efficacy Evaluation

11.2.1 Demographics and Other Baseline Values

This will provide an overview of subjects as well as summary statistics for demographic variables (e.g. gender and age), disease factors (e.g. complications and medical history), and

other potentially related factors.

11.2.2 Analysis Set for Efficacy Evaluation

The primary analysis set for this clinical trial, the Full Analysis Set (FAS), will consist of all subjects registered in the trial, excluding those for whom the following is applicable:

- Subjects with serious departures from good clinical practice (GCP)
- Subjects for whom the study drug is not administered even once
- Subjects for whom efficacy evaluations are never conducted

Additionally, subjects for whom the following criteria are applicable will be excluded from the FAS to create the Per Protocol Set (PPS, analyses using the PPS will be conducted to confirm the robustness of the results of analyses using FAS):

- Subjects who do not meet the selection criteria or those who violate the exclusion criteria
- Subjects for whom the study drug administration period was less than 26 weeks
- Subjects for whom the study drug administration rate was less than 70%.

Efficacy in this clinical trial will be evaluated with the total cases using FAS and PPS. Further evaluation will be performed with no L-arginine Co-Administration and L-arginine Co-Administration cases separately.

Furthermore, as subjects suitable for a more appropriate evaluation of the efficacy of this drug, main analyses will also be conducted using the following subjects from FAS/PPS:

- Subjects in which at least two stroke-like episodes are confirmed in the 78-week period before consent is obtained (i.e., those meeting the MELAS stroke diagnostic criteria).

- Secondary evaluations will also be conducted with the following patients:
- Subjects in whom focal neurological signs (with no consideration of high-intensity signals detected by brain MRI) are confirmed at least two times in the 78-week period before consent is obtained and those in whom focal neurological signs are confirmed at least once with the presence of high-intensity lesion(s) using diffusion-weighted brain MRI.
- Subjects in whom focal neurological signs (with no consideration of high-intensity lesion(s) observed with diffusion-weighted brain MRI) are confirmed at least two times in the 78-week period before consent is obtained.
- Subjects in whom at least two stroke-like episodes meeting the MELAS stroke diagnostic criteria are confirmed in the 52-week period before consent is obtained.
- Subjects in whom focal neurological signs (with no consideration of high-intensity lesion(s) observed with diffusion-weighted brain MRI) are confirmed at least two times in the 52-week period before consent is obtained.

11.2.3 Efficacy Endpoint Analysis Method

(1) Primary Endpoint Analysis Method

Primary analysis: Based on the Clopper-Pearson method, an exact 95% confidence interval will be assumed. Secondary analysis: The effect of the study drug and background parameters on the percentage of 100% responders will be evaluated using logistic regression analysis. A confidence interval of 95% for the 100% responder rate based on the Clopper-Pearson method will be assumed for the total cases. It will be further assumed for no L-arginine Co-Administration and L-arginine Co-Administration cases separately.

(2) Secondary Endpoint Analysis Method

An exact 95% confidence interval will be assumed based on the Clopper-Pearson method for the 50% responder rate. The effect of the study drug and background parameters on the percentage of 100% responder rate will be evaluated using logistic regression analysis. An exact 95% confidence interval based on the will be assumed for the total cases. It will be further assumed for no L-arginine Co-Administration and L-arginine Co-Administration cases separately.

For each measurement point, summary statistics will be calculated for clinical symptoms (mitochondrial disease severity score), blood and CSF taurine, lactate, and pyruvic acid levels, and lactate/pyruvic acid ratio. Summary statistics will be calculated for before and after the clinical trial for the number of abrupt-onset focal neurological deficits (not regarding confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI) observed, number of times intravenous arginine is used before and after the study drug administration, and number of times high-intensity lesion(s) are confirmed with diffusion-weighted brain MRI based on the appearance of headaches, nausea/vomiting, convulsions, and/or impaired consciousness.

Additionally, time, study drug, time and study drug interaction, and other background parameters will be evaluated for their association with changes in each parameter over time as necessary, using a marginal or mixed model.

11.3 Safety Evaluation

11.3.1 Analysis Set for Safety Evaluation

Analyses will be conducted with the group of registered subjects for whom the study drug has been administered at least once. This includes subjects who experience adverse events

and those who are later determined to have violated the exclusion criteria after study drug administration.

11.3.2 Safety Endpoint and Analysis Method

Incidence for all and individual adverse events and side effects that are observed in this clinical trial.

12. Clinical Trial Method

12.1 Registration of Subjects

Subjects will be registered by the central registration method.

(1) For subjects that meet the selection criteria and do not violate the exclusion criteria, the principal (sub) investigator will explain the details of the clinical trial using the consent/explanatory documents and request participation, and subjects who give consent will be registered.

(2) Registration will be conducted by entering the necessary items into the electronic data capture (EDC) system. After registration, a subject identification code will be automatically assigned.

(3) The principal (sub) investigator will begin administration of the study drug for subjects determined to be eligible.

(4) The principal (sub) investigator will enter and save the automatically assigned subject identification code to the “Subject Identification Code List.”

12.2 Discontinuation or Interruption of a Trial

12.2.1 Criteria for Discontinuation or Interruption of a Trial

In the event of any of the following, determined by either the coordinating investigator or those implementing the trial independently from the medical institutions, whether or not the clinical trial should be continued in its entirety or at one medical facility will be investigated:

(1) If information on the quality of the study drug, items relating to its efficacy or safety, or other critical information relevant for the suitability of the clinical trial is learned.

(2) If modifications to the clinical trial protocol are required, and the medical institution(s) at which the trial is being implemented cannot provide support the trial.

(3) If there is a modification of the instructions in the clinical trial protocol, etc. from the director of the medical institution at which it is being implemented based on the opinion of the IRB, and the coordinating investigator or those participating in the trial independently cannot agree to it.

(4) If the director of the medical institution(s) at which the trial is being implemented instructs the discontinuation of the trial based on the decision of the IRB.

(5) If the medical institution at which the trial is being implemented conducts a serious or continuing breach of GCP or the clinical trial protocol. The principal investigator of each institution will promptly report to the coordinating investigator if the trial at their facility is discontinued. Additionally, if this trial is discontinued or interrupted, it will be promptly reported to the coordinating investigator and explained in detail.

12.2.2 Discontinuation or Interruption of the Entire Trial

If the coordinating investigator or an individual conducting the trial independently decides

to discontinue or interrupt the entire trial, the director of the medical facility at which the trial is being implemented and the regulatory authority will be promptly informed of this decision, with disclosure of the reason in writing. If the director of the institution at which the trial is being implemented receives this notice from the coordinating investigator or individual conducting the trial independently, they will promptly inform the IRB of this decision, with disclosure of the details.

If the clinical trial is interrupted or discontinued, the principal investigator will promptly inform the subjects and ensure that they receive proper treatment.

Correspondence with subjects in the event of the clinical trial discontinuation will be conducted in accordance with the “Discontinuation Procedures” in Section 10.2.

12.2.3 Discontinuation or Interruption of a Trial at a Medical Institution by the Institutional Review Board

If the IRB decides to interrupt or discontinue the clinical trial, the director of the medical institution at which the trial is being implemented will be promptly informed of this in writing, including the details of the reason(s). The director of the medical institution will promptly inform the principal investigator and coordinating investigator of this in writing.

13. Case Reports

13.1 Format of Case Reports

In this clinical trial, an electronic case report utilizing an EDC system will be used. An electronic case report, for which the contents are confirmed and electronically signed by the principal investigator, will be treated as the original. CD-Rs from the electronic case reports at

the institutions implementing the trial will be created, copied, and stored. (The electronic case file that is electronically signed by the principal investigator will be saved as a PDF).

13.2 Material Entered Directly into the Case Report and Materials that Should Be Used as Original Data

Of the data entered into the case report, the following items will be used as original data:

(1) Purpose of concomitant drugs and purpose of concomitant treatments

(2) Adverse events (severity, degree, outcome, day of outcome, and reason for classifying a causal relationship with the study drug)

(3) Day of discontinuation, reason for discontinuation, adverse event that caused the discontinuation, progression, and follow-up results after discontinuation

(4) Principal (sub) investigator comments.

13.3 Notes on Case Report Writing

Case reports will be created by the principal (sub) investigator or personnel collaborating with the trial, according to the following specifications:

(1) Prior to entering information into the case report, an individual in charge of data management will issue the principal (sub) investigator/collaborating personnel with a user ID and password and will manage users. Each individual who receives a username and password will manage only that account. Accounts will not be shared.

(2) Case reports will be created for subjects to whom the study drug is administered.

(3) Data input will be conducted by those with input privileges—the principal (sub)

investigators and collaborating personnel. Principal investigators will be able to work on every item of the case report. Sub-investigators will be able to work on every item of the case report other than the electronic signature. Coordinating personnel will be able to transcribe from other sources such as the medical records and transcribe items not involving medical decisions from the original sources.

(4) In the event of changes or corrections to the case report, the reason for the change or correction will be recorded electronically.

(5) After confirming the accuracy and integrity of the case report, with reference to the audit history and electronic signature information, the principal investigator will electronically sign the case report form in the EDC system.

(6) The principal investigator will take custody of a copy (the electronic case report with the contents confirmed by the principal investigator saved as a PDF) of the saved (CD-R, etc.) case report form. After it is electronically signed, for the period before a CD-R, etc. is provided, the individual in charge of data management will substitute it with a duplicate through the provision of a browsing environment (EDC system access privileges).

(7) If there is any contradiction with the original source in the data recorded in the case report, the principal investigator will create a record explaining the reason, submit it to the individual in charge of data management, and save a copy.

14. Compliance with Ethical Principles

This clinical trial will be implemented in compliance with the ethical principles of the Declaration of Helsinki, pharmaceutical affairs law, and GCP, in addition to this clinical trial

protocol.

15. Institutional Review

15.1 Approval of the Institutional Review Board

Before this clinical trial is conducted, the IRBs of the medical institutions at which the trial will be implemented will examine and approve the clinical trial protocol, the details of the information in the consent/explanatory documents for subjects, and the appropriateness of the trial from the standpoints of ethical, scientific, and medical validity.

15.2 Review for Trial Continuation

For the purpose of continuing the clinical trial, the principal investigator will report to the IRB once per year regarding the status of the clinical trial, and the continuation of the trial will be subject to review.

Additionally, if information is obtained that will necessitate a secondary IRB investigation related to the continuation of the trial, or if a serious modification to the clinical trial protocol is made, it will be reported to the IRB, and the continuation of the trial will be subject to review.

16. Trial Protocol Compliance, Deviation, Change, and Revision

16.1 Compliance with Trial Protocol

The principal (sub) investigator will implement the clinical trial in compliance with this clinical trial protocol.

16.2 Deviations from and Changes to Trial Protocol

Principal (sub) investigators cannot deviate from or change the clinical trial protocol without obtaining prior written approval based on a review from the IRB. However, deviation from, or changes to, the clinical trial protocol without prior approval from the IRB will be allowed in circumstances where there is medically no other choice, such as the presence of an urgent risk to the subjects. In that case, if the deviation or modification details and reasoning as well as the amendments to the trial protocol are appropriate, the principal investigator will submit a draft to the director of the medical institution and the IRB as quickly as possible. IRB approval, written acknowledgement from the director of the medical institution, and approval from the coordinating investigator will be required.

Principal (sub) investigators will be required to record all conduct that deviates from the clinical trial protocol. The principal investigator will be required to submit a written record of the rationale directly to the director of the medical institution and the coordinating investigator and save a copy only if a deviation from the clinical trial protocol is implemented when there is medically no other choice, such as to the presence of urgent risk to the subjects.

If any changes to the clinical trial will seriously influence the implementation of the trial or increase risk to the subjects, the principal investigator will submit a written report promptly to the director of the medical institution, the IRB, and the coordinating investigator.

16.3 Revisions to Trial Protocol

If a modification to the trial protocol is found to be necessary during the trial by the

coordinating investigator or those independently conducting the trial, the trial protocol will be revised. The coordinating investigator or those independently conducting the trial will promptly inform the director of the medical institution of the details of the revision in writing, and approval from the IRB will be obtained by the director of the medical institution.

If the director of the medical institution is instructed to modify the trial protocol based on the opinion of the IRB, the coordinating investigator and/or those independently conducting the trial will revise the trial protocol as necessary. The director of the medical institution will be promptly informed of the details of the revision in writing, and approval from the IRB will be obtained by the director of the medical institution.

16.4 Provision of New Information

If the coordinating investigator or those conducting the trial independently obtain information indicating that the study drug will have a negative effect on the safety of the subject, information that can influence the implementation of the trial, or information that will necessitate a secondary investigation related to the continuation of the trial by the IRB, the director of the medical institution will be promptly informed in writing.

If new information that is necessary to convey to the subjects is obtained, those conducting the trial independently will modify the consent/explanatory documents promptly and obtain approval from the IRB.

17. Direct Access to Trial Material

The principal investigator or the director of the institution assures that upon receiving an inquiry from those monitoring the coordinating investigator or those independently

conducting the trial, auditors, the IRB, or regulatory authorities, they will be guaranteed direct access to all materials relating to the trial.

18. Quality Control and Quality Assurance of the Trial

The coordinating investigator and/or those conducting the trial independently must conduct quality control and quality assurance for the purpose of maintaining the quality and reliability of the trial. Additionally, the medical institution(s) must cooperate in trial quality control and quality assurance, according to the coordinating investigator and/or those independently conducting the trial.

For quality control of the trial, source materials will be directly monitored, and procedural documents relating to trial operations at the medical institutions and compliance with the latest trial protocols and GCP will be confirmed as appropriate. Additionally, the accuracy and integrity of the details of case reports prepared by the principal (sub) investigator will be ensured with reference to the source material, including trial-related records.

Additionally, audits will be performed by those in charge in accordance with the procedural manual that will confirm that appropriate quality control measures are practiced to guarantee that the trial is being conducted in compliance with the clinical trial protocol and GCP.

19. Costs Related to Trial Participation

Medical treatment related expenses, excluding the drugs that have the same efficacy and effect as the expected efficacy and effect of the investigational medicinal product during the clinical trial, shall be covered by health insurance treatment. Expenses for trial collaboration

will be paid in accordance with the specifications of each medical institution. The study drug used in this clinical trial will be supplied by the provider free of charge.

20. Compensation for Injury

In the event of injury to the subject, the medical institution implementing the trial will provide the necessary support such as medical care and perform the necessary and appropriate treatment. At that time, if the injury occurs from the appropriate use of the study drug, and the principal investigator identifies a causal relationship with the study drug, the burden of the compensation costs will fall on the principal investigator. If the injury is determined to be due to the injured subject's deliberate or gross negligence, they may not be eligible for compensation.

In observance of the contract measures, in the event that liability arises because of an injury resulting from the clinical trial, the coordinating investigator will provide insurance for the coordinating investigator, principal investigator, sub investigator, and the medical institution. Additionally, the principal investigator and sub investigator will have physician liability insurance, and the medical institutions will have hospital liability insurance.

21. Record Keeping

21.1 Storage of Records for Trials at Medical Institutions

The record keeper appointed by the head of the medical facility will save the necessary documents and records relating to the trial for the medical facility until a later date, as specified in (1) or (2) below. However, if the coordinating investigator, or those implementing the study independently from any of the medical institutions, sees it necessary

to save them for a longer period, the medical facility will discuss the preservation period and method with the coordinating investigator/those independently implementing the study.

Additionally, in the event that the provider of the study drug decides not to approve request form, the head of the medical facility will be informed of this and the reason in writing.

1) The manufacturing and marketing approval date for the study drug (alternatively, the discontinuation of development, or three years past the day notice is received that the clinical trial results will not be sent with the approval request form).
2) Three years past the day that the clinical trial is discontinued or completed.

If the study drug provider receives manufacturing and marketing approval, or if approval is not received and the development is discontinued, this will be reported to the head of the medical facility in writing.

21.2 Storage of Records for Those Conducting the Trial on Their Own

Those carrying out the trial on their own will save the necessary documents and records relating to their trial until a later date as specified in 1) or 2) below. The study drug provider will be consulted for correspondence after the end of the storage period.

(1) The manufacturing and marketing approval date for the study drug (alternatively, the discontinuation of development, or if notice is received that the clinical trial results will not be sent with the approval request form and development is discontinued, or three years past the day notice is received that they will not be sent with the request form).
(2) Three years past the day that the clinical trial is discontinued or completed.

If the study drug provider receives manufacturing and marketing approval, or if approval is not received and the development is discontinued, this will be reported to the head of the medical facility in writing.

22. Protection of Confidentiality and Personal Information

Subject registration and case reports will be created with subject-specific subject identification codes and protection of personal information in such a way that subjects cannot be identified and will be given full consideration for direct access to raw data relating to the trial, subject consent forms, etc. and the publication of the research results. Personal information obtained from subjects for this clinical trial will not be disclosed to third parties.

23. Publication and Attribution of the Clinical Trial Results

The information (data, etc.) from this clinical trial, or any portion thereof, cannot be published by any method without prior permission of the coordinating investigator, those participating in the trial independently, and the study drug provider.

24. Trial Organization

24.1 Coordinating Investigator

Responsible for the management and supervision of this clinical trial:

Professor Sunada Yoshihide

Kawasaki Medical School, Department of Neurology

TEL: 086-462-1111 (Ext. 27507)

FAX: 086-464-1027

24.2 Coordinating Executive Officer

Coordination of operations for management of this clinical trial:

Professor Sunada Yoshihide

Kawasaki Medical School, Department of Neurology

TEL: 086-462-1111 (Ext. 27507)

FAX: 086-464-1027

24.3 Trials Conducted at Medical Institutions and by Individual Principal Investigators

See KN01 Study Investigators in the supplementary appendix.

24.4 Study Drug Provider

Taisho Pharmaceutical Co., Ltd. (Tokyo, Japan) provided good manufacturing practice-grade taurine.

24.5 Development of Outsourcing Institution and Laboratory

See attached sheet (Attachment 1).

24.6 Trial Costs

This clinical trial will be conducted through the Health, Labor, and Welfare Grant-in-Aid for Scientific Research: Overcoming Intractable Diseases Research Program (H24-Nanchitou(Nan)-Ippan-068).

25. References

1) Yasukawa T, Suzuki T, Suzuki T, et al. Modification defect at anticodon wobble nucleotide of mitochondrial tRNAsLeu(UUR) with pathogenic mutations of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. J Biol Chem 2000;275:4251-7

2) Yasukawa T, Suzuki T, Ishii N, et al. Wobble modification defect in tRNA disturbs codon-anticodon interaction in a mitochondrial disease. EMBO J 2001;20:4794-802

3) Rikimaru M, Ohsawa Y, Wolf AM, et al. Taurine ameliorates impaired the mitochondrial function and prevents stroke-like episodes in patients with MELAS. Int Med 2012;3351-7

4) Yatsuga S, Povalko N, Nishioka J, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Act 2012;1820:619-24

5) Davidson MM, Walker WF, Hernandez-Rosa E. The m.3243A>G mtDNA mutation is pathogenic in an in vitro model of the human blood brain barrier. Mitochondrion 2009;9:463-70

6) Kamata T, Koizumu T, Kozima J, et al. A double-blind, placebo-controlled clinical evaluation of taurine in acute hepatitis. Sulfur Amino Acids 1980;3:223-35 (in Japanese)

7) Matsuzaki Y, Tanaka N, Osuga T. Is taurine effective for treatment of painful muscle cramps in liver cirrhosis? Am J Gastroenterol 1993;88:1466-7

8) Nomoto M, Izumi K, Tominaga H, et al. Efficacy of taurine in tardive dyskinesia and essential tremor. Sulfur Amino Acids, 1983;6:47-51

Attachment 1. Date of Creation: 7/9/2013

24.3 Site Institutions and Clinical Trial Implementing Parties (Investigators)

24.3.1 Site Institutions and Clinical Trial Implementing Parties (Investigators)

Kawasaki Medical School Hospital, Neurology, Yoshihide Sunada (Department Director), 577 Matsushima, Kurashiki-shi, Okayama-ken, 701-0192, Japan, Phone: 086-462-1111

National Defense Medical College Hospital, Division of Neurology, Anti-aging, and Vascular Medicine, Hiroyuki Onoue (Appointed Lecturer), 3-2 Namiki, Tokorozawa-shi, Saitama-ken 359-8513, Japan, Phone: 04-2995-1511

Seirei Hamamatsu General Hospital, Neurology, Tsuyoshi Uchiyama (Department Director), 2-12-22 Sumiyoshi, Naka-ku, Hamamatsu-shi, Shizuoku-ken, 430-8558, Japan, Phone: 053-474-2222

Fujita Health University Hospital, Neurosurgery Department, Prof. Tatsuro Mutoh, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake-shi, Aichi-ken 470-1192, Japan, Phone: 0562-93-2111

National Hospital Organization Kyoto Medical Center, Internal Medicine of Neurology, Michikazu Nakamura (Head Physician), 1-1 Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto-shi, Kyoto-fu, 612-8555, Japan, Phone: 075-641-9161

Hyogo-Chuo National Hospital, Internal Medicine of Neurology, Katsuya Nishida, 1314 Ohara, Sanda-shi, Hyogo-ken, 669-1592, Japan, Phone: 079-563-2121

Fukuoka University Chikushi Hospital, Department of Pediatrics, Prof. Atsushi Ogawa, 1-1-1 Zokumyoin, Chikushino-shi, Fukuoka-ken, 818-8502, Japan, Phone: 092-921-1011

Kurume University, Medical School Hospital, Prof. Yasutoshi Koga, 67 Asahi-machi, Kurume-shi, Fukuoka-ken, 830-0011, Japan, Phone: 0942-35-3311

Nagasaki University Hospital, Internal Medicine of Neurology, Hirokazu Shiraishi 1-7-1 Sakamoto, Nagasaki-shi, Nagasaki-ken, 852-8501, Japan, Phone: 095-819-7200

Jichi Medical University Hospital, Internal Medicine of Neurology, Lecturer, Haruo Shimazaki, 3311-1 Yakushiji, Shimotsuke-shi, Tochigi-ken, 329-0498, Japan, Phone: 0285-44-2111

[Main Tasks]

As the lead party responsible for the team of subinvestigators, trial collaborators and other members, the investigators are charged with managing and directing as well as heading the tasks related to this clinical trial at the site institutions.

24.3.2 Research Organization

Kawasaki Medical School, Department of Neurology, Prof. Yoshihide Sunada

[Research duties that are shared] Support for conclusions and serious adverse events

Kawasaki Medical School, Department of Neurology, Yutaka Osawa (Lecturer)

[Research duties that are shared] Support for data management

Kawasaki Medical School, Department of Neurology, Assoc. Prof. Tatsufumi Murakami

[Research duties that are shared] Support for personal information

Teikyo University of Science, Faculty of Medicine, Prof. Hiroki Hagiwara

[Research duties that are shared] Support for monitoring and authorities

National Center of Neurology and Psychiatry, Department of Mental Retardation and Birth Defect Research, Yuichi Gotoh (Department Director)

[Research duties that are shared] Support for registry

Kurume University, Medical School Hospital, Prof. Yasutoshi Koga

[Research duties that are shared] Support for monitoring and auditing

Kawasaki Medical School, Molecular Biology I (Embryology), Shinichiro Nishimatsu (Lecturer)

[Research duties that are shared] Support for specimens and intellectual properties

Graduate School of Nippon Medical School, Aging Science, Prof. Shigeo Ohta

[Research duties that are shared] Support for specimens and intellectual properties

24.4 Investigational Medicinal Product Suppliers

Taisho Pharmaceutical Co., Ltd.

3-24-1 Takada, Toshima-ku, Tokyo, 103-0024, Japan

Phone: 03-3985-1111

[Main Tasks]

The following duties are carried out based on the consultation with coordinating investigators and investigators.

1) The investigational medicinal product is provided to the investigational product administrator established by the investigators or the directors of the site institutions.
2) Information such as the safety information related to the investigational medicinal product is collected and provided.

24.5 Contract Research Organization and Testing Organization

24.5.1 Contract Research Organization

(1) Project Management

CTD Inc.

3-3-2 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan

Phone: 03-6228-4105 Fax: 03-6228-4843

Responsible party: Fumiaki Kobayashi

Associates in charge: Kazuo Watanabe and Mai Moriyama

[Main Tasks]

The trial coordinating agency provides support based on instructions from the coordinating investigator.

(2) Monitoring

DOT WORLD CO., LTD.

PMO Hatchobori Building 3-22-13 Hatchobori , Chuo-ku, Tokyo, 104-0032, Japan

Phone: 03-3523-0210 Fax: 03-3523-0225

Responsible Party: Tetsuya Orito

Clinical Research Associates: Namiko Murao, Keiko Onodera, Naoko Kataoka, Ayumi Kuramoto, Miho Araki

[Main Tasks]

Follow procedures according to separately created documents and conduct monitoring.

(3) Auditing

SRD Co., Ltd.

RBM Kyobashi Building 3-4-8 Hatchobori, Chuo-ku, Tokyo, 104-0032, Japan

Phone: 03-5543-0297 Fax: 03-5543-0184

Responsible Party: Seichi Ooba

Associates in charge: Yuki Shoji, Taka Kubota

[Main Tasks]

An audit is conducted following a procedure that is created separately, in order to check the suitability of the trial system and the reliability of the data for this study.

(4) Data Management

DOT WORLD CO., LTD.

PMO Hatchobori Building 3-22-13 Hatchobori, Chuo-ku, Tokyo, 104-0032, Japan

Phone: 03-3523-0210 Fax: 03-3523-0225

Responsible Party: Tatsuhiro Uenishi

Associate in charge: Atsushi Koda

Part of these duties is re-contracted to Takumi Information Technology Inc.

[Main Tasks]

1) Preparations for data management (Creating data input screen, creating input manual, creating data management plan, creating code rules, creating check list for data input)

2) Providing feedback for discrepancies in data (logical checks, issuing queries)

3) Coding (Adverse events, concomitant drugs, etc.)

(5) Statistical Analysis

DOT WORLD CO., LTD.

PMO Hachobori Building 3-22-13 Hachobori, Chuo-ku, Tokyo, Japan, 104-0032

Phone: 03-3523-0210 Fax: 03-3523-0225

Responsible Party: Tatsuhiro Uenishi

Associate in charge: Atsushi Koda

Part of these duties is re-contracted to Takumi Information Technology Inc.

[Main Tasks]

The Statistical Analysis Plan is created following the analysis method noted in the Protocol, and the calculation and analysis is carried out following that plan. However, the duties are discussed and reviewed with the person in charge of data management.

(6) Medical Writing

DOT WORLD CO., LTD.

PMO Hatchobori Building 3-22-13 Hatchobori, Chuo-ku, Tokyo, 104-0032, Japan

Phone: 03-3523-0210 Fax: 03-3523-0225

Responsible Party: Mayumi Saotome

Associates in charge: Chie Arai, Ryo Yano

[Main Tasks]

Preparation of the Clinical Study Report (Draft).

24.5.2 Testing Organization

(1) Blood WBC: Measurement of $tRNA^{Leu(UUR)}$ taurine modification rate

Kawasaki Medical School, Molecular Biology I

577 Matsushima, Kurashiki-shi, 701-0192, Japan

Phone: 086-462-1111 Ext. 78078

Associates in charge: Shinichiro Nishimatsu

(2) Blood WBC: Measurement of mitochondrial DNA mutation rate, ND6 protein level

Nippon Medical School – Institute of Gerontology, Cell Biology

1-396 Kosugimachi, Nakahara-ku, Kawasaki-shi, Kanagawa-ken, 211-8533, Japan

Phone: 044-733-9267

Associate in charge: Shigeo Ohta

(3) Measurement of lactic acid (in blood and CSF), pyruvic acid (in blood and CSF), amino acid analysis (in blood and CSF)

SRL Medisearch Inc.

Shinjuku I-Land-Tower 10F, 6-5-1, Nishishinjuku, Shinjuku-ku, Tokyo 163-1310, Japan

Phone: 03-5324-2602 Fax: 03-5324-3508

Responsible party: Katsuhiro Ikeoka

Measurement Organization:

SRL Inc.

2-1-1 Nishishinjuku, Shinjuku-ku, Tokyo 163-0409, Japan

Phone: 03-6279-0900

Responsible party: Yoji Hirabayashi

[Main Tasks]

1) Specimens are collected.

2) The specimens are measured.

3) The specimen results report and the coordinating tasks are conducted.

Attachment 2: MELAS Diagnosis Criteria Date of Creation: 6/28/2013

MELAS Diagnosis Criteria was originally created by Koga Group (a Research Grant from the Ministry of Health, Labour and Welfare of Japan, March 2005; Yatsuga S, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Acta 2012;1820:619-24).

◆**Recognition Criteria / Certain Cases**

Cases that meet item 2 in the clinical findings for apoplexy in A. and meet item 2 for the rationale of mitochondria abnormalities below (Minimum of 4 items in total required).

A. Clinical Findings for Apoplexy

1. Headache and vomiting
2. Convulsion
3. Hemiplegia
4. Homonymous hemianopsia or cortical blindness
5. Acute local abnormal finding of the brain in brain image Note 1

B. Rationale for Mitochondrial Abnormality

1. Lactic acid level in blood and CSF is repeatedly high, or absence of mitochondria related enzyme Note 2
2. Malformation of mitochondria in muscle biopsy Note 3
3. (MELAS related) Already known gene mutation Note 4

Note 1. Local brain lesions exist in brain imaging such as head CT or MRI.

Note 2: When lactic acid levels in the blood and pyruvic acid in the CSF while resting in bed is ≥2 mmol/L (18 mg/dL), or when the enzymes are absent in a cell-based (preferably muscular tissue) enzyme search such as electron transport chain enzymes, pyruvate metabolism related enzymes, TCA cycle related enzymes or lipid metabolism related enzymes.

Note 3: Muscle pathology, such as ragged-red fiber (RRF for Gomori trichrome staining: ragged-red fibers), RRF or SSV (strongly SDH -reactive blood vessels) in succinate dehydrogenase staining or cytochrome-c oxidase deficient fiber, mitochondria morphological defects found using electron microscope, etc.

Note 4: The already known DNA mutations that have been reported as genes that cause MELAS exists (Such as mitochondria tRNA-Leu(UUR) genes A3243G, G3244A, A3252G, A3260G, T3271C and T3291C, and mitochondria tRNA-Val gene G1642A, mitochondria tRNA-Cys gene A5814G, mitochondria COX gene T9957C, mitochondria ND5 gene G13513A mutations)

Attachment 3: The Japanese Mitochondrial Disease Rating Scale (JMDRS)

Date of Creation 6/19/2013

The Japanese Mitochondrial Disease Rating Scale (JMDRS) was originally created by Koga Group (a Research Grant from the Ministry of Health, Labour and Welfare of Japan, March 2005; Yatsuga S, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Acta 2012;1820:619-24), which was modified from the European Neuromuscular Conference mitochondrial disease scale. The European.[Note 1]

Ages that can be assessed: 6 years old and older.

◆Section 1: activities of daily living

A. Speech

0-normal

1-mildly affected, no difficulty being understood

2-moderately affected, may be asked to repeat

3-severely affected, frequently asked to repeat

4-unintelligible most of time

B. Swallowing

0-normal

1-rare choking

2-occasional choking

3-requires soft food

4-requires nasogastric or gastrostomy tube

C. Handwriting

0-normal

1-slightly small or slow

2-all words small but legible

3-severely affected, not all words legible

4-majority illegible

D. Cutting food- handling utensils

0-normal

1-somewhat slow and clumsy but no help needed

2-can cut most foods, some help needed

3-food must be cut, but can feed self

4-needs to be fed

E. Dressing

0-normal

1-somewhat slow and clumsy but no help needed

2-occasional helps with buttons or arms in sleeves

3-considerable help required but can do some things alone

4-helpless

F. Hygiene

0-normal

1-somewhat slow and clumsy but no help needed

2-needs help with shower or bath or very slow in hygienic care

3-requires assistance for washing, brushing teeth, going to bathroom

4-helpless

G. Falling

0-none

1-rare falling

2-less than one per day

3-average of once per day

4-more than one per day

H. Paroxysmal event (migraine, seizures)

0-none

1-<1every1month

2->1every1month<1every week

3->1every1week<1every day

4->1every day/status, Status epilepticus

◆Section 2: motor

A. Proximal muscle strength (modified MRC)

0-normal

1-slight reduction of power (grade4 MRC, MRC4)

2-moderate impairment, able to overcome gravity (MRC3)

3-severe weakness, unable to overcome gravity (MRC2)

4-severe weakness, flicker only (MRC1)

5-no voluntary muscle activity (MRC0)

B. Upper limb coordination

Modified ICARS, International Cooperative Ataxia Rating Scale.

0-normal

1-mild clumsiness- no significant disability

2-moderate clumsiness- poor writing, able to perform ADL

3-severe clumsiness- unable to write

4-severe clumsiness- unable to feed

C. Walking

0-no limitation

1-limited a little (getting tired after 1-2 km)

2-moderately limited (difficulties keeping up with friends)

3-severe limited (having to stop every 100-400m to rest)

4-no walking distance beyond 10m

D. Moderate motor activities

(such as vacuum cleaning, carrying groceries, climbing one flight of stairs , preparing your bed)

0-no limitation

1-limited a little

2-moderately limited

3-severely limited

4-not capable

E. Vigorous motor activities

(such as running, climbing several flights of stairs, or participating on other strenuous sports)

0-no limitation

1-limited a little

2-moderately limited

3-severely limited

4-not capable

◆Section 3: special sensory

A. Vision

0-normal

1-unable to drive or equivalent (i.e. unable to read traffic or shop signs)

2-unable to read normal print books

3-unable to read standard large print books

4-unable to watch TV

5-no useful vision

B. Auditory

0-< 10dB loss

1-0-20 dB loss

2-20-40 dB loss

3-severe >40 dB but improves with hearing aid

4-severe >40 dB loss and does not improve with hearing aid

◆Section 4: endocrine

0-normal

1-single endocrine organ involvement

2-2 endocrine organs involved

3-3 endocrine organs involved

For diabetes, add 1 for insulin treated

◆Section 5: cardiac

0-normal ECG and ECHO

1-conduction system disease, mild impaired LV function (EF >60%)or asymptomatic hypertrophy

2-ECHO evidence of cardiomyopathy and restricted physical activity (EF <60%) or cardiac pacemaker

3-Moderate cardiomyopaty (EF <40-60%)

4-Severe cardiomyopaty

◆Section 6: Renal function[Note 2]

0-Normal

1-Creatine clearance <50-90 ml/min/1.73 m^2

2-Creatine clearance 30-50 ml/min/1.73 m^2

3-Creatine clearance 10-30 ml/min/1.73 m^2

4-Creatine clearance <10 ml/min/1.73 m^2 or dialysis in needed

◆**Section 7: cognition and impairment**

A. Intellectual impairment

0-normal

1-mild (consistent forgetfulness with partial recollection of events with no other difficulties)

2-moderate memory loss with disorientation and moderate difficulty handing complex problems

3-severe memory loss with disorientation to time and often place, severe impairment with problems

4-severe memory loss with orientation only to person, unable to make judgments or solve problems

B. Motivation and drive

0-normal

1-lacking in energy, does not restrict activities

2-lacking in energy, restricts hobbies and interests

3-lacking in energy, restricts day to day (routine) activities

4-unable to carry out any task

Note 1: In the ENMC (Chinnery PF, Bindoff LA. Europen neuromuscular center. 116th ENMC international workshop: the treatment of mitochondrial disorders, 14th-16th March 2003, Naarden, The Netherlands. Neuromuscul Disord 2003;13:757-64.), the target age was assumed to be adults, and in the Japanese version, the target age is stated because it includes children's ages as well.

Note 2: Section 6 - Renal function has been added in the Japanese version

KN-01
Medication Diary

Please bring this sheet at the next visit.

Next Visit：

Month:　　, Day:　　, Year: 201　

【Precaution of medication】

- Please take medicine (KN-01) three times a day after meals.
- If you forgot to take KN-01, please take it when you remember. Please take the next dose at the usual time (after meals). Please do not take KN-01 twice at once.
- We are planning to ask you the exact time you took the last meal on your next visit.

Your Name:_____

【Contact Information】

Medical Institution:

_____

Principal Investigator:

_____

Attending Doctor:

_____

CRC:

_____

Contact Information:

TEL: _____

In the case of nighttime / holiday,
you should call the emergency
outpatient with the same phone number.

【Example】

Medication Day	Morni		ng
2013 y. 10 m. 02 d.	■ (8 :00)	■ (12:00)	■ (19:00)
2013 y		■ (12:00)	■ (19:00)
2013 y		■ (12:00)	■ (19:00)
2013 y. 10 m. 04 d.	■ (8 :00)		
2013 y. 10 m. 05 d.	■ (8 :00)		
2013 y. 10 m. 06 d.	■ (8 :00)		
2013 y. 10 m. 07 d.	■ (8 :00)	■ (12:00)	■ (19:00)
2013 y. 10 m. 08 d.	■ (8 :00)	■ (12:00)	■ (19:00)
2013 y. 10 m. 09 d.	■ (8 :00)	■ (12:00)	■ (19:00)
2013 y. 10 m. 10 d.	■ (8 :00)	■ (12:00)	□ (:)
2013 y. 10 m. 11 d.	□ (:)	□ (:)	:)
2013 y. 10 m. 12 d.	□ (		)
2013 y. 10 m. 13 d.	□ (		)
2013 y. 10 m. 14 d.	□ (		)

Please fill out the medication time.

Please fill out the medication day.

If you forget to take medication, it will be unchecked.

If the next visit date is October 10, 2013, 14 o'clock, please have a statement before noon on the day and come to the hospital.

If you take medicine from today until the next visit, please check.

Medication method： 3 times a day,

□ capsules once (□ gram) after meals

Medication Day	Morning	Noon	Evening
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
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If you take medicine from today until the next visit, please check.

Medication method : 3 times a day,

□ capsules once (□ gram) after meals

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If you take medicine from today until the next visit, please check.

Medication method : 3 times a day,

□ capsules once (□ gram) after meals

Medication Day	Morning	Noon	Evening
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201__y. __m. __d.	□ (:)	□ (:)	□ (:)

If you take medicine from today until the next visit, please check.

Medication method :   3 times a day,

□ capsules once (□ gram) after meals

KN01 Multicenter Trial Focusing on

Mitochondrial Encephalomyopathy (MELAS)

Clinical Trial Protocol

Coordinating Investigator

Kawasaki Medical School

Department of Neurology

Sunada Yoshihide

Date of Creation: 12/5/2013

Clinical Trial Protocol Number: KN01-MELAS-01

Version Number: Version 2.0

Table of Contents

1. Summary of Clinical Trial Protocol

Trial title	KN01 Multicenter Trial Focusing on Mitochondrial Encephalomyopathy (MELAS)
Objective	Implementation of taurine therapy as a suppressive treatment for recurrent stroke-like episodes in MELAS patients and an examination of its efficacy and safety.
Subjects	Patients that meet all of the following inclusion criteria and do not violate the exclusion criteria.
Inclusion criteria	(1) Patients with a comprehensive and definitive diagnosis of MELAS who meet the criteria for MELAS based on clinical manifestations, muscle pathology, and genetic screening. (2) Patients who show any of the following point mutations in mitochondrial DNA: A3243G, T3271C, G3244A, T3258C, or T3291C. (3) Age, gender, and hospitalization/outpatient status will not be inquired at the time of consent. (4) Patients who have not used L-arginine within the 78-week period before consent is obtained or those who have been using L-arginine for a minimum of 26 weeks prior to consent. (5) Patients who meet the following criteria for stroke-like episodes* before consent is obtained: ① Patients who are not using L-arginine: at least two stroke-like episodes within the 78-week period before consent and at least one stoke-like episode within the 52-week period before consent are

	obtained. ② Patients who are using L-arginine and meet any of the following criteria during the period of L-arginine use: (i) If the period of L-arginine use is 78 weeks or less, at least two stroke-like episodes within that period and at least one stroke-like episode within the 52-week period before consent is obtained. (ii) If the period of L-arginine use is more than 78 weeks, at least two stroke-like episodes within the 78-week period before consent and at least one stroke-like episode within the 52-week period before consent is obtained. *A stroke-like episode for the selection criteria is defined as the presence of any of the following abrupt-onset focal neurological deficits (with no consideration of brain magnetic resonance imaging [MRI] use): ① Hemiparesis or monoparesis ② Cortical sensory deficit (extinction) ③ Cortical visual deficit (scintillating scotoma or cortical blindness) ④ Aphasia ⑤ Apraxia ⑥ Agnosia (6) Patients with no history of oral taurine treatment.

	(7) Patients capable of judging the clinical manifestations of a stroke-like episode. (8) Individuals for whom informed consent for participation in this clinical trial is obtained in writing by the patients themselves before enrollment. (For minors, individuals for whom written consent is obtained from a legal guardian, and written assent is obtained from the patient themselves for participation in this clinical trial).
Exclusion criteria	(1) Patients who cannot undergo brain MRI, such as those with pacemakers. (2) Patients with status epilepticus or those in severe coma. (3) Patients with dementia, those who are bedridden, or those with whom communication is not possible. (4) Patients with concomitant sepsis. (5) Patients with severely impaired cardiac, hepatic, or renal function. (6) Patients who require systemic administration of steroids for 2 weeks or longer. (7) Patients who have used pyruvic acid within the 12-month period before consent is obtained. (8) Patients who are breast feeding, pregnant, or may become pregnant. (9) Patients with a history of hypersensitivity to the components of

<table>
<tr><td></td><td>the study drug.
(10) Patients with a history of drug allergies.
(11) Patients who have participated in a clinical trial within the 12-month period before consent is obtained.
(12) Patients who are determined to be ineligible as subjects for other reasons by the principal investigator or sub-investigator.</td></tr>
<tr><td>Target number of subjects</td><td>15 subjects</td></tr>
<tr><td>The study drug</td><td>(1) Clinical study drug ID: KN01
(2) Generic name: Taurine
(3) Ingredients and dosage form: 1 g of taurine in 1.02 g powder</td></tr>
<tr><td>Dosage and administration method</td><td>The daily amount of the study drug, determined by patient body weight categories below, will be administered orally three times daily after meals.
<table><tr><td>Weight*</td><td>Amount per day</td></tr><tr><td>40 kg or more</td><td>12 g</td></tr><tr><td>25–39 kg</td><td>9 g</td></tr><tr><td>15–24 kg</td><td>6 g</td></tr><tr><td>Less than 15 kg</td><td>3 g</td></tr></table>* Body weight before the observation period</td></tr>
<tr><td>Administration period</td><td>52 weeks</td></tr>
<tr><td>Disallowed concomitant treatments and drugs</td><td>(1) Pyruvic acid, (2) steroids with systemic administration for 2 weeks or longer, and (3) oral L-arginine (in patients who are not taking oral L-arginine at the start of the clinical trial)</td></tr>
<tr><td>Allowed concomitant</td><td>(1) Medications that the principal investigator or sub-investigator</td></tr>
</table>

drugs	determine to be necessary may be used. However, the medication name, dosage and administration method, administration period, and reason for concomitance will be described in the case report. (2) Emergency treatment drugs: no limit (includes intravenous L-arginine). (3) Drugs that can be used during the trial period with limited changes to the dosage and administration: nitric acid, vasodilators with nitric oxide inducers, coenzyme Q, antiepileptic drugs (if taken continuously since the pretrial period), and oral L-arginine (if taken for 26 weeks or more before consent is obtained).
Observation, examination, and examination items	(1) Clinical symptoms (number of stroke-like episodes and mitochondrial disease severity score) (2) Physical examination (weight, temperature, blood pressure, and pulse) (3) Blood tests (hematological tests and biochemical examinations) (4) Specialized blood tests: Blood lactate (deproteinized), blood pyruvic acid (deproteinized), and blood amino acid analysis (39 types) Cerebrospinal fluid (CSF) examination (optional): CSF lactate (deproteinized), CSF pyruvic acid (deproteinized), and CSF amino acid analysis (39 types) Blood leukocyte examination (optional): Mitochondrial gene mutation rate, $tRNA^{Leu(UUR)}$ taurine modification rate, and NADH dehydrogenase 6 protein mass (5) Imaging (brain MRI)

	(6) Mini-Mental State Examination (MMSE) score
Evaluation items	(1) Efficacy Efficacy in this clinical trial will be evaluated with total subjects, and either subjects with L-arginine Co-Administration or no L-arginine Co-Administration. ① Primary end point: Percentage of subjects with no stroke-like episodes (100% responder rate) during the evaluation period (from 9 weeks after the start of study drug administration to the end of administration). ② Secondary end points: (i) Mitochondrial disease severity score (Japanese Mitochondrial Disease Rating Scale [JMDRS]) (ii) 50% responder rate (iii) Number of abrupt-onset focal neurological deficits defined in the MELAS stroke diagnostic criteria (with no consideration of confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI) (iv) Specialized tests (blood and CSF levels of taurine, lactate, and pyruvic acid and lactate/pyruvic acid ratio) (v) Imaging (brain MRI examination) (vi) Number of times intravenous L-arginine is administered both before and after administration of the study drug (vii) Number of times the patient experiences headache, nausea/vomiting, convulsions, or impaired consciousness with confirmation of high-intensity signal(s) by brain MRI

	(2) Safety, adverse events, and side effects
Clinical trial period	September 2013–December 2014

2. Background Information and Trial Significance

Mitochondrial myopathy, encephalopathy, lactic-acidosis, and stroke-like episodes (MELAS) is the most frequent mitochondrial disease. One base substitution in the $tRNA^{Leu(UUR)}$ gene coded by mitochondrial DNA is proposed to be the underlying cause of MELAS; however, the exact pathologic mechanism remains to be elucidated. MELAS follows an aggressive course, with recurring stroke-like episodes and damage accumulating in the central nervous system. Currently, treatment includes mitigation of cerebral infarction in acute phase of disease and improvement of energy metabolism during the chronic course of disease. However, such treatment approaches are not sufficient; therefore, the most serious clinical presentation of MELAS that needs to be urgently addressed for the development of an effective therapeutic modality is the recurrence of stroke-like episodes. Our group was the first to discover a deficiency in anticodon taurine modification of the mutant mitochondrial $tRNA^{Leu(UUR)}$ in MELAS.[1] This taurine modification plays an important role in codon recognition for translation. We previously revealed that this taurine modification deficit led to the failure of protein synthesis in MELAS and proposed that the fundamental pathology underlying MELAS was an RNA modification disorder.[2] Furthermore, taurine supplementation to cells in culture in an *in vitro* MELAS model led to the improvement of mitochondrial function.[3] Based on these original fundamental observations, recurrent stroke-like episodes were completely suppressed for more than nine years in two patients with MELAS that were orally administered taurine.[3] Based on these results, this clinical trial will be conducted as a physician-led clinical trial of the Health, Labor, and Welfare Grant-in-Aid for Scientific Research: Overcoming Intractable Diseases Research Program

(Funded by the Ministry of Health, Labor, and Welfare of Japan, H24-Nanchitou(Nan)-Ippan-068).

3. Objectives

This clinical trial will utilize taurine supplementation therapy as treatment for the suppression of recurrent stroke-like episodes in patients with the rare, incurable disease, MELAS, and examine its efficacy and safety.

4. Trial Protocol

4.1 Trial Schedule

4.1.1 Investigation Period

Case registration period: September 2013–December 2013

Investigation period: September 2013–December 2014

4.1.2 Participation Period

Period before observation: 7 days

Period of study drug administration: 52 weeks

(1) Patients who are confirmed to be eligible after informed consent is obtained will be registered.

(2) The study drug will be administered for 52 weeks, during which time the number and severity of stroke-like episodes will be determined.

4.1.3 Trial Methods

The trial will be conducted as a multicenter, open-label, phase 3 trial.

Rationale for trial design: A highly reliable, randomized, double-blind, placebo-controlled trial is not ethically possible in patients with MELAS as the average life expectancy after diagnosis is only 7.3 ± 5.0 years.[4]

4.2 Subjects

Patients who meet all of the following inclusion criteria and do not violate the exclusion criteria will be subjects of this clinical trial.

4.2.1 Inclusion Criteria

(1) Patients with a comprehensive and definitive diagnosis of MELAS who meet the Japanese MELAS diagnostic criteria (Ministry of Health, Labour and Welfare Research Group, Koga Group, 2005) based on clinical manifestations, muscle pathology, and genetic screening.[4]

(2) Patients who have any of the following point mutations in mitochondrial DNA: A3243G, T3271C, G3244A, T3258C, or T3291C.

(3) Age, gender, and hospitalization/outpatient status will not be inquired at the time of consent.

(4) Patients who have not used L-arginine within the 78-week period before consent is obtained or those who have been using L-arginine for a minimum of 26 weeks prior to consent.

(5) Patients who meet the following criteria for stroke-like episodes* before consent is obtained:

① Patients who are not using L-arginine: at least two stroke-like episodes within the 78-week period before consent is obtained and at least one stroke-like episode within the 52-week period before consent is obtained.

② Patients who are using L-arginine and meet any of the following criteria during the period of L-arginine use:

(i) If the period of arginine use is 78 weeks or less, at least two stroke-like episodes within that period and at least one stroke-like episode within the 52-week period before consent is obtained.

(ii) If the period of L-arginine use is more than 78 weeks, at least two stroke-like episodes within the 78-week period before consent and at least one stroke-like period within the 52-week period before consent is obtained.

*A stroke-like episode for the selection criteria is defined as the presence of any of the following abrupt-onset focal neurological deficits (with no consideration of confirmation by brain MRI):

① Hemiparesis or monoparesis

② Cortical sensory deficit (extinction)

③ Cortical sensory deficit (scintillating scotoma or cortical blindness)

④ Aphasia

⑤ Apraxia

⑥ Agnosia

(6) Patients with no history of oral taurine treatment.

(7) Patients capable of judging the clinical manifestations of a stroke-like episode.

(8) Individuals for whom informed consent for participation in this clinical trial is obtained in writing by the patients themselves before enrollment. (For minors, individuals for whom written consent is obtained from a legal guardian, and written assent is obtained from the patient themselves for participation in this clinical trial).

Rationale for inclusion criteria:

(1) In order for this trial to be comprehensive, MELAS diagnosis will be determined based on multiple parameters, such as clinical manifestations, genetic testing, and muscle pathology.

(2) As evaluation of the efficacy of the study drug on mitochondrial gene mutation rate is a planned outcome of this trial, MELAS patients with the indicated mutations will be chosen as subjects.

(3) As both males and females can be subjects, gender will not be inquired. As both hospitalized and outpatient patients can be subjects, status will not be inquired. As stroke-like episodes occur in high frequency in both children and adults, it is possible that the efficacy of the study drug will be observed in subjects regardless of age, gender, or hospitalization/outpatient status.

(4) Patients not using L-arginine and those using L-arginine will be both chosen as subjects.

(5) This trial is designed to include patients with stoke-like episodes within the indicated time periods to allow for sufficient assessment of the efficacy of the study drug chosen.

(6) To avoid any potential confounding effects of prior taurine treatment on the outcomes of the current clinical trial, patients with a history of taurine supplementation will not be enrolled.

(7) As the primary end point is the number of stroke-like episodes, patients should to be able to recognize the clinical manifestations.

(8) As emergency measures may be necessary during a stroke, only patients whose consent is obtained before enrollment will be chosen as subjects. Furthermore, participation in this clinical trial will be decided by the free will of the patient themselves, and for

minors, themselves and a legal guardian. In the event of difficulty to obtain consent from the patient, those patients for whom written consent is obtained from a legal guardian will be chosen as subjects.

4.2.2 Exclusion Criteria

(1) Patients who cannot undergo brain MRI, such as those with pacemakers.

(2) Patients with status epilepticus or those in severe coma.

(3) Patients with dementia, those who are bedridden, or those with whom communication is not possible.

(4) Patients with concomitant sepsis.

(5) Patients with severely impaired cardiac, hepatic, or renal function.

(6) Patients who require systemic administration of steroids for 2 weeks or longer.

(7) Patients who have used pyruvic acid within the 12-month period before consent is obtained.

(8) Patients who are breast feeding, pregnant, or may become pregnant.

(9) Patients with a history of hypersensitivity to the components of the study drug.

(10) Patients with a history of drug allergies.

(11) Patients who have participated in a clinical trial within the 12-month period before consent is obtained.

(12) Patients who are determined to be ineligible as subjects for other reasons by the principal investigator or sub-investigator.

Rationale for exclusion criteria:

(1) As stroke-like episodes in this clinical trial will be assessed by brain MRI, patients

who cannot be evaluated by brain MRI will be excluded.

(2) Efficacy of the study drug might be impossible to determine for these patients as they cannot report symptoms due to impaired consciousness.

(3) With the progression of dementia, patients will be increasingly unlikely to report symptoms, hindering determination of efficacy. Additionally, this exclusion criterion is included for ethical and safety reasons.

(4) Patients with concomitant sepsis will be excluded to maintain their safety.

(5) This exclusion criterion is for the safety of patients.

(6) Steroids promote vasoconstriction and reduce vascular endothelial function and can adversely impact the efficacy evaluation of the study drug.

(7) Pyruvic acid has been reported to improve the symptoms of mitochondrial disease by lowering lactate levels, which may confound the efficacy evaluation of the study drug.

(8–11) These criteria are indicated to maintain the safety of patients.

(12) This criterion is indicated to account for factors other than those indicated in (1–11) that may influence the assessment of the study drug.

4.3 Target Number of Subjects

15 subjects.

Rationale for target number of subjects: The target number of subjects are determined based on the following feasibility and statistical review-related factors:

・ During the planning phase for this clinical trial, the results of three nationwide surveys focusing on neurology and pediatrics indicated that the estimated potential number of enrollees (i.e. those with two or more stroke-like episodes within the past year) were 21

subjects for the L-arginine Co-Administration and 5 subjects for the no L-arginine Co-Administration. All the subjects that meet the remaining inclusion criteria, do not violate the exclusion criteria, and provide consent will be enrolled. The actual number of subjects recruited is feasible in consideration of the expected trial period.

- Taurine administered in two MELAS patients led to the complete suppression of recurrent stroke-like episodes for more than nine years.[3] Because of the small number of patients, the 100% expected responder rate from these results are conservatively estimated as 50%.
- In patients currently being treated with off-label L-arginine, the number of stroke-like episodes almost never reaches zero. Therefore, as achievement of no stroke-like episodes after the study drug administration is an objective indicator showing treatment efficacy, the 100% responder rate was adopted as the primary endpoint.
- The subjects of this clinical trial will be patients who have had at least two stroke-like episodes in the 78-week period before consent is obtained. Of those currently being treated with off-label L-arginine, those subjects with no stroke-like episodes are few and far between. Therefore, the threshold 100% responder rate is estimated as 5%.
- For a hypothesis of a threshold 100% responder rate of 5% and an expected 100% responder rate of 50% when 15 subjects are integrated, we can ensure a power of 90% or above with a 5% two-sided significance. Furthermore, we can ensure a power of 80% or more with ten subjects in the no L-arginine Co-Administration and five patients in the L-arginine Co-Administration.
- Efficacy in this clinical trial will be evaluated with the total cases. Further evaluation will be performed with no L-arginine Co-Administration and L-arginine Co-Administration subjects separately.

5. The Study Drug

5.1 The Study Drug

Study drug ID: KN01

Generic name: Taurine

Ingredients and dosage form: 1 g of taurine in 1.02 g, powder

Dosage and administration method: The total daily dose of the study drug, determined by patient body weight categories indicated below, will be administered orally three times daily after meals.

Weight*	Amount per Day
40 kg or more	12 g
25–39 kg	9 g
15–24 kg	6 g
Less than 15 kg	3 g

*Body weight before the observation period

5.2 Handling of the Study Drug

The study drug will be issued once the provision of the study drug is agreed upon between the coordinating investigator and the study drug provider. The study drug manager will assure the storage and management of the study drug in accordance with the procedural manual for administration of the study drug that is created by those participating in the trial independently. Upon completion of the trial, the coordinating investigator will recover any unused drug and packaging. The study drug shall not be used for any purpose other than this clinical trial.

6. Dosage and Administration

6.1 Dosage and Administration Method

The daily amount of the study drug, determined by patient body weight categories indicated below, will be administered orally three times daily after meals.

Weight*	Amount per Day
40 kg or more	12 g
25–39 kg	9 g
15–24 kg	6 g
Less than 15 kg	3 g

*Body weight before the observation period

Rationale for dosage and administration:

In this clinical trial, the taurine dose will be 12 g per day divided into three doses, which is higher than the dose for the currently approved indications for taurine, hyperbilirubinemia, and congestive heart failure, which is 3 g per day divided into three doses. The decision to exceed the previously approved dosage is based on the following factors indicating that 12 g per day (divided into three doses) is the highest taurine dose that is possible to confirm as safe with potential efficacy.

(1) In a single-dose toxicity test (rabbit, intravenous administration) and repeated dose toxicity/reproductive and developmental toxicity test (rat, oral administration), the no-observed-adverse-event level was 1,000 mg/kg or more.

(2) As a mouse model of MELAS does not exist,[5] we cannot assess the potential deficit improvements with taurine treatment in a model mouse as a preclinical study; thus, we must refer to previous clinical studies.

(3) The safety and efficacy of 12 g of taurine per day was confirmed in patients with hyperbilirubinemia.[6]

(4) No serious adverse events or side effects were reported in two previous reports of

off-label use of taurine.

① One study reported safe oral administration of 6 g/day taurine three times daily for 6 months in 12 patients with muscle cramps resulting from non-alcoholic cirrhosis.[7]

② One study reported safe oral administration of 6 g/day taurine three times daily (taken after each meal) for 14 days in five patients with essential tremor for more than 15 years.[8]

(5) A previous study on taurine treatment in patients with MELAS confirmed the safety and efficacy of 12 g/day taurine divided into three doses.[3]

(6) In two patients with MELAS who are currently undergoing continuous treatment with taurine, the safety and efficacy of the administration method and dosage to be used in this clinical trial, 12 g per day (divided into three doses) has been confirmed.

(7) In pediatric patients, although taurine supplementation was administered for other indications, in a study of 33 individuals with ages ranging from infancy to the age of 16 years, subjects were administered between 0.5 g and 6 g taurine per day. Among a total of 28 cases with information on side effects, no taurine-associated side effects were observed.

6.2 Administration Period

The administration period will be 52 weeks.

Rationale for administration period:

Based on previous research on taurine treatment in MELAS and the status of MELAS patients currently undergoing continuous administration, an administration period of 52 weeks is determined sufficient for adequate assessment of its efficacy.

6.3 Allowed and Disallowed Concomitant Treatments and Drugs

6.3.1 Disallowed Concomitant Drugs

1) Pyruvic acid

2) Oral L-arginine (patients who are not taking oral L-arginine at the start of the clinical trial)

Rationale:

(1) Oral L-arginine is disallowed based on studies demonstrating its vasodilatory effect and efficacy in stroke prevention, which may confound the accurate assessment of the efficacy of the study drug. There is a risk that it may augment or hinder the effect of the study drug.

(2) Oral L-arginine is disallowed after the start of the clinical trial because of the potential impact on the assessment of the efficacy of the study drug.

6.3.2 Disallowed Concomitant Treatments

Steroid treatments:

Systemic administration of steroids for 2 weeks or longer is prohibited.

Rationale:

As steroids promote vasoconstriction and reduce vascular endothelial function, concomitant use of steroids can adversely impact the efficacy evaluation of the study drug.

6.3.3 Allowed Concomitant Drugs and Treatments

Medication that the principal investigator or sub-investigator determine to be necessary may be used. However, the medication name, dosage and administration, administration period, and reason for concomitance will be described in the case report.

・Emergency treatment drugs:

No limit (includes intravenous L-arginine)

・Drugs that can be used during the trial period, limiting changes to the dose or administration as much as possible:

Nitric acid, vasodilators with nitric oxide inducers, coenzyme Q, anti-epileptic drugs (if taken continuously since the pretrial period), and oral L-arginine (if taken for 26 weeks or more before consent is obtained).

Rationale

For drugs used in emergencies, lifesaving treatment must be the priority, and limiting their use is difficult. Consequently, the use of emergency treatment drugs will not be limited, and the use of intravenous L-arginine will be allowed. Nitric acid, vasodilators with nitric oxide inducers, coenzyme Q, and antiepileptic drugs are medications conventionally used for MELAS prevention. As their discontinuation would be problematic, their use is permitted as long as significant changes in their dosage and administration are avoided, if possible. For orally administered L-arginine, its use is permitted for patients who have been using it for at least 26 weeks before the beginning of the study drug administration and will continue using it after the beginning of the trial. Any changes to the dosage and administration method of L-arginine in these patients will be limited if possible, to control its effects on the determination of efficacy for the study drug.

7. Observations, Evaluation Items, and Time Period

7.1 Observation and Examination Schedule

Observations and examinations will be conducted in accordance with the following schedule.

Table 1. Observation/Examination/Evaluation Schedule

		Consent	Period Before Observation		Observation Period						Discontinuation
			-1 week		0 week		4 weeks	12 weeks	24 weeks	36 weeks	52 weeks	
Day			-7～0		0		28	84	168	252	364	
Acceptable Range (Days)							± 7	± 7	± 14	± 14	± 14	
Consent Obtained		●										
Patient Background Survey[1]			●									
Brain MRI			●[2]					●[3]			●	●
Registration				●								
Observation of Number of Stroke-Like Episodes								●[4]				●[4]
MELAS Severity[5] (12-Lead echocardiogram [ECG])					●						●	●
Physical Examination[6]					●		●	●	●	●	●	●
In Hospital Blood Testing[7]	Hematological Tests				●		●	●	●	●	●	●
	Biochemical Tests				●		●	●	●	●	●	●
Specialized Testing	Blood Tests[8]				◎		◎				◎	◎
	CSF Tests[9]				◎						◎	◎
	Blood Leukocyte Tests[9]				◎						◎	◎
MMSE Score					●						●	●
Study Drug Prescription						●	●	●	●	●		
Study Drug Compliance Check						●	●	●	●	●	●	●
Adverse Events Check						●	●	●	●	●	●	●
Co-Administered[10] Drug/Treatment Survey[10)]		●	●		●		●	●	●	●	●	●

● Hospital implementation/measurement item, ◎: Centralized facility measurement item

1) The following items will be examined:

① Patient gender, birth date, and age;

② Number of stroke-like episodes in the past 78-week period (and L-arginine co-administration period for the L-arginine co-administration);

③ Mitochondrial DNA mutation points (A3243G, T3271C, G3244A, T3258C, T3291C);

④ Blood pressure, pulse, height, and weight;

⑤ Complications and smoking history;

⑥ Medical history of the 78-week period before consent is obtained.

2) Brain MRI scans obtained within the 4-week period before the start of study drug administration can be used.

3) Brain MRI scans will be obtained when stroke-like episodes occur.

4) The occurrence of the stroke-like episodes will be confirmed. The stroke-like episode will be determined in accordance with the MELAS stroke diagnostic criteria: Fulfillment of both ① and ②:

① Any of the following abrupt-onset focal neurological deficits:

(1) Hemiparesis or monoparesis

(2) Cortical sensory impairment (elimination of sensation)

(3) Cortical sensory impairment (scintillating scotoma or cortical blindness)

(4) Aphasia

(5) Apraxia

(6) Agnosia

② Confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI.

5) MELAS severity will be determined in accordance with the Japanese mitochondrial disease rating scale (JMDRS).

6) Weight, temperature, blood pressure, and pulse while sitting at rest.

7) Hematology: red blood cell count, leukocyte count, platelet count, hemoglobin level, hematocrit level, and hemogram.

Biochemical Examination: total protein, albumin, glucose, hemoglobin A_1c (HbA_1c) value, aspartate transaminase (AST, GOT), alanine transaminase (ALT, GPT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (γ-GTP), creatine kinase (CK), total bilirubin (T-Bil), direct bilirubin (D-Bil), blood urea nitrogen (BUN), creatinine (Cre), uric acid, triglycerides (TG), total cholesterol (T-Cho), Na, K, Cl.

8) Blood test: blood lactate (deproteinized), blood pyruvic acid (deproteinized), and blood amino acid analysis (39 types) will be measured with SRL.

Cerebrospinal fluid (CSF) examination: CSF lactate (deproteinized), CSF pyruvic acid (deproteinized), and CSF amino acid analysis (39 types) will measured with SRL.

Blood leukocyte examination: mitochondrial gene mutation rate, $tRNA^{Leu(UUR)}$ taurine modification rate, and NADH dehydrogenase 6 protein mass will be measured at the Kawasaki Medical School/Japan Medical Institute for the Elderly.

9) Optional

10) Information, co-administration period, and reason for co-administration for drugs and treatments used since the 4-week period before consent until the end of the observational period will be surveyed.

7.1.1 Observation of Stroke-Like Episodes and their Severity

(1) Observation of Stroke-Like Episodes

Stroke-like episodes will be determined based on the following MELAS stroke diagnostic criteria

Table 2. MELAS stroke diagnostic criteria: Fulfillment of both ① and ②

① Any of the following abrupt-onset focal neurological deficits:

(1) Hemiparesis or monoparesis

(2) Cortical sensory deficit (extinction)

(3) Cortical sensory deficit (scintillating scotoma or cortical blindness)

(4) Aphasia

(5) Apraxia

(6) Agnosia

② Confirmation of high-intensity signal(s) with diffusion-weighted brain MRI.

It should be noted that if a new lesion is found by brain MRI even in the presence of multiple abrupt-onset focal neurological deficits, if the lesion is confirmed by brain MRI within 2 weeks of the signs, they will be counted as one episode. Additionally, if the lesion appears within 2 weeks of a previous stroke-like episode, a lesion confirmed by brain MRI will be considered as part of the same episode.

In addition to the abrupt-onset focal neurological deficits measured by the MELAS stroke diagnostic criteria, the presence of the following symptoms will be recorded:

(1) Headache

(2) Nausea and vomiting

(3) Convulsions

(4) Impaired consciousness

(2) MELAS Degree of Severity

Prior to the start of the study drug administration and at the time of discontinuation after 52 weeks of treatment, the MELAS degree of severity will be determined in accordance with the Japanese mitochondrial disease rating scale (JMDRS; Ministry of Health, Labour and Welfare Research Group, Koga Group, 2005) that is adopted with modifications from the European Neuromuscular Conference (ENMC) mitochondrial disease rating scale (2003).

Note that, at the time of evaluation of subjects for MELAS degree of severity, 12-lead electrocardiography and echocardiography (ejection fraction [EF], left ventricular diastolic dimension [LVDD], left ventricular systolic dimension [LVSD], pulse wave Doppler [PWD], tricuspid regurgitation peak gradient [TRPG], asynergy, and valve) will be conducted. The estimated glomerular filtration rate (eGFR) will be calculated based on the following formula:

$$eGFR\ (mL/min/1.73\ m^2) = 194 \times Cr^{-1.094} \times age^{-0.287}\ (male)$$

$$eGFR\ (mL/min/1.73\ m^2) = 194 \times Cr^{-1.094} \times age^{-0.287} \times 0.739\ (female).$$

7.1.2 Physical Examination

The following measurements will be taken prior to the start and after 4, 12, 24, 36, and 52 weeks (at the time of discontinuation) of the study drug administration:

(1) body weight

(2) body temperature

(3) blood pressure and pulse (at rest while sitting)

7.1.3 In-Hospital Blood Tests

These tests will be performed prior to the start and after 4, 12, 24, 36, and 52 weeks (at the time of discontinuation) of the study drug administration. A specific time of day for blood collection is not specified. However, the amount of time that has elapsed since the previous meal and the time of previous administration of the study drug will be recorded.

Hematological tests: red blood cell count, leukocyte count, platelet count, hemoglobin level, hematocrit level, and hemogram.

Biochemical Examinations: total protein, albumin, glucose, hemoglobin A_1c (HbA_1c), aspartate transaminase (AST, GOT), alanine transaminase (ALT, GPT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma-glutamyl transferase (γ-GTP), creatine kinase (CK), total bilirubin (T-Bil), direct bilirubin (D-Bil), blood urea nitrogen (BUN), creatinine (Cre), uric acid, triglycerides (TG), total cholesterol (T-Cho), Na, K, Cl.

7.1.4 Specialized Tests

These evaluations will be conducted at a centralized facility. A specific time of day for blood and CSF collection is not specified. However, the amount of time that has elapsed since the previous meal and the time of previous administration of the study drug will be recorded.

(1) SRL Measurement (by SRL Medisearch Inc., Tokyo, Japan)

Prior to the start and after 4 and 52 weeks (at the time of discontinuation) of the study drug administration:

Blood tests: blood lactate (deproteinized), blood pyruvic acid (deproteinized), and blood amino acid analysis (39 types).

Prior to the start and after 52 weeks (at the time of discontinuation) of the study drug administration:

CSF examination (optional): CSF lactate (deproteinized), CSF pyruvic acid (deproteinized), and CSF amino acid analysis (39 types).

(2) Measurements at Kawasaki Medical School/Japan Medical School for the Elderly

Prior to the start and after 52 weeks (at the time of discontinuation) of the study drug administration:

Peripheral blood leukocyte examination (optional): mitochondrial gene mutation rate, mitochondrial $tRNA^{Leu(UUR)}$ taurine modification rate, and NADH dehydrogenase 6 protein mass.

7.1.5 Imaging

Prior to the start and after 52 weeks of the study drug administration (at the time of discontinuation) and in the presence of a stroke-like episode defined by the MELAS stroke diagnostic criteria ①, brain MRI will be conducted. The imaging method will be as follows: diffusion-weighted image (axial), magnetic resonance angiography (MRA) image (intracranial), fluid-attenuated inversion recovery (FLAIR) image (axial), T2-weighted image (axial), T1-weighted image (axial), and T2*-weighted image (axial). Additionally, if possible, an apparent diffusion coefficient (ADC) map will be calculated. MRI scans accompanying stroke-like episodes will be conducted as quickly as possible, but it is essential that they are performed within 2 weeks after the occurrence of the event at most.

7.1.6 MMSE Score

MMSE scores will be determined prior to the start and after 52 weeks (at the time of discontinuation) of the study drug administration.

7.2 Patient Characteristics

The following items will be determined prior to the start of the study drug administration:

(1) Patient gender, birth date, and age

(2) Items related to the stroke-like episodes that occurred within the 78-week period before consent is obtained:

① Number

② Length

③ Diagnostic results of brain MRI studies (only if one was conducted)

④ Status of intravenous L-arginine use

(3) Brain MRI findings (brain MRIs obtained within the 4-week period before the start of study drug administration is acceptable)

(4) Mitochondrial DNA point mutations (A3243G, T3271C, G3244A, T3258C, T3291C)

(5) Blood pressure, pulse, height, and weight

(6) Complications, smoking history

(7) Medical history for the 78-week period* before consent is obtained.

*For patients continuing the use of oral L-arginine, the period of oral L-arginine use (26 weeks or more, up to 78 weeks)

7.3 Determination of Efficacy Endpoints

7.3.1 Primary Endpoint for Efficacy (100% responder rate)

The primary endpoint is the percentage of cases with no stroke-like episodes (100% responders) during the evaluation period (between 9 weeks after the start of study drug administration and the time of its discontinuation).

Rationale for 100% responder rate as the primary endpoint: In patients currently being treated with off-label L-arginine, the number of stroke-like episodes almost never reaches zero. Therefore, as achievement of no stroke-like episodes after the study drug administration is an objective indicator showing treatment efficacy, the 100% responder rate was adopted as the primary endpoint.

Stroke-like episode diagnosis method

Stroke-like episodes will be diagnosed based on the MELAS stroke diagnostic criteria defined below.

Table 3. MELAS stroke diagnostic criteria: Fulfillment of both ① and ②

① Any of the following abrupt-onset focal neurological deficits:

1) Hemiparesis or monoparesis

2) Cortical sensory deficit (extinction)

3) Cortical sensory deficit (scintillating scotoma, cortical blindness)

4) Aphasia

5) Apraxia

6) Agnosia

② Confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI.

It should be noted that a new lesion found by brain MRI even in the presence of multiple abrupt-onset focal neurological deficits, if the lesion is confirmed by brain MRI within 2 weeks of the signs, will be counted as one episode. Additionally, if the lesion appears within 2 weeks of a previous stroke-like episode, a lesion confirmed by brain MRI will be considered part of the same episode.

Stroke-like episode evaluation period

(1) Subjects for no L-arginine Co-Administration:

Stroke-like episodes will be compared between the following:

Before the start of the trial: the 78-week period before consent is obtained

and

After the start of the trial: the period between 9 weeks after the start of the study drug administration and the end of administration (first 8 weeks after the start of the study drug administration will not be included in the evaluation period).

(2) Subjects for L-arginine Co-Administration:

Stroke-like episodes will be compared between:

Before the start of the trial: the period of L-arginine treatment before consent is obtained (26 weeks or more, up to 78 weeks)

and

After the start of the trial: the period between 9 weeks after the start of the study drug administration and the end of administration (first 8 weeks after the start of the study

drug administration will not be included in the evaluation period).

Rationale for the diagnosis of stroke-like episodes in this trial:

As there are no diagnostic criteria for MELAS stroke-like episodes in adults, the new MELAS stroke diagnostic criteria are established in this study. There is a stroke scale for pediatric patients with MELAS (Ministry of Health, Labor, and Welfare Research Group, Koga Group, 2005); however, as it includes items such as headache, nausea/vomiting, convulsions, and impaired consciousness that can result from etiologies other than stroke, it is excluded from the diagnostic criteria. As the present diagnostic criteria are specifically aimed at distinguishing items with a causal relationship to stroke, a stroke-like episode is established as the presence of idiopathic focal neurological signs and confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI.

Rationale for the evaluation period for stroke-like episodes in this trial:

(1) Subjects for no L-arginine Co-Administration:

The evaluation period before the administration of the study drug is set as the maximum period possible for evaluation, the 78-week period before consent is obtained. The evaluation period after administration of the study starts at 9 weeks after the start of the study drug administration; the first 8 weeks are excluded from evaluation, as the effects of the study drug are not expected to manifest for a period of time at the beginning of its administration.

(2) Subjects for L-arginine Co-Administration:

The evaluation period before the administration of the study drug is set to 78 weeks before consent is obtained. As the period of L-arginine use is not expected to be consistent across subjects, to standardize the L-arginine Co-Administration in this clinical trial, the period of

L-arginine use is required to be a minimum of 26 weeks before consent is obtained, and this period is set as the evaluation period before the administration of the study drug. L-arginine dose modification during this period is acceptable.

The evaluation period after the start of the study drug administration is the same as that for the no L-arginine Co-Administration group. As a general rule, the L-arginine dose is not changed after the start of the study drug administration.

7.3.2 Secondary Endpoints for Efficacy

(1) Improvement of clinical symptoms

Clinical symptoms will be evaluated according to the JMDRS criteria (Ministry of Health, Labor, and Welfare Research Group, Koga Group, 2005; Appendix 2)

(2) 50% responder rate

The percentage of cases with 50% or more reduction in stroke-like episodes for each 4 weeks of the evaluation period after the start of study drug administration, in comparison with the number of stroke-like episodes before its administration.

(3) Number of abrupt-onset focal neurological deficits defined by the MELAS stroke diagnostic criteria (with no consideration of confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI).

(4) Specialized testing (blood/CSF taurine, lactate, and pyruvic acid levels, and lactate/pyruvic acid ratio)

(5) Imaging studies (brain MRI scans)

(6) Number of times intravenous L-arginine is used before and after the start of study drug administration.

(7) Number of times high-intensity lesion(s) are confirmed with diffusion-weighted brain MRI in the presence of headache, nausea/vomiting, convulsions, or impaired consciousness.

Rationale for secondary endpoints in this clinical trial:

(1) A previous study[3] showed that clinical symptoms improved after taurine treatment.

(2) The percentage of subjects with 50% reduction in the number of stroke-like episodes is chosen as a clinically significant endpoint.

(3) Only abrupt-onset focal neurological deficits are chosen, and confirmation by the presence of high-intensity lesion(s) with diffusion-weighted brain MRI will not be necessary.

(4) In a previous study,[3] blood/CSF taurine, lactate, and pyruvic acid levels, and lactate/pyruvic acid ratio increased after taurine treatment.

(5) In a previous study,[3] abnormal signals that reflect stroke-like episodes by brain MRI disappeared after taurine treatment.

(6) Changes in the status of intravenous L-arginine use will be assessed, as its use as emergency treatment for stroke-like episodes is expected.

(7) MRI findings will be assessed for symptoms other than the neurological symptoms defined by the MELAS stroke diagnostic criteria.

7.4 Safety Evaluation Items

7.4.1 Evaluation Items

(1) Subjective symptoms/objective findings (including worsening of complications)

(2) Physical examination

(3) Clinical examination

7.4.2 Handling of Vital Signs and Laboratory Test Values

If the vital signs and clinical laboratory values deviate from the standard, the abnormal values will be recorded in the case report. The clinical examination items will use the standards of measurement used by each institution for each item, and the standard values from the following “Vital Signs Standard Values” chart will be used for vital signs.

Note that these will not be treated as laboratory abnormalities as defined in Section 9.2.1 “Definition of Adverse Events.”

<Vital Signs Standard Values>

Blood Pressure (mmHg)	Systolic Blood Pressure Standard Value: 90–140
	Diastolic Blood Pressure Standard Value: 50–90
Pulse (beats per minute)	Standard Value: 50–110
Temperature (°C)	Standard Value: 35–37°C

Values recorded after the start of the study drug administration will be compared to those recorded before the start of the study drug administration to determine if there are any abnormal variations in each measurement. The range of physiological variation in each patient and its clinical significance will be considered based on this determination. In this case, regardless of the presence of a change from a normal value to an abnormal value or from an abnormal value to worsening of an abnormal value, if abnormal variation is deemed

not present, the reason for this decision will be recorded in the medical record. Additionally, if there is an item with a missing value at the beginning of the study drug administration, if every subsequent value is within the abnormal range, this item will be treated as an abnormal variation.

The degree of abnormal variation (severity) will be determined with reference to the 80th issue of the Ministry of Health and Welfare Pharmaceutical Affairs Bureau Division Notification on Pharmaceuticals, "Severity classification criteria for side effects of pharmaceuticals, etc." However, the definitions for group 1, group 2, and group 3 defined in the 80th issue will correspond to the definitions of mild, moderate, and severe, respectively, in this trial.

When abnormal variation is found, it will be treated as an adverse event and follow-up will be performed if necessary. However, even when abnormal variation is not found, items determined to be adverse events by either the principal investigator or sub-investigator will be treated as adverse events, and follow-up will be performed if necessary. Follow up will be conducted in accordance with the procedures defined in section 7.4.3 "Follow-Up."

If the principal investigator or sub-investigator determines the adverse event to be causally related to the study drug—in reference to the causal relationship criteria defined in Section 9.2 "Dealing with Adverse Events"—it will be recorded in the case report. The range of physiological variation for each examination item and combined treatments, etc. will be considered in the decision-making. If the study drug is determined not to be causally related to abnormal variations, the rationale will be recorded in the case report.

In addition to the abovementioned steps, evaluation items that are not measured but are determined to be adverse events by the principal investigator or sub-investigator will be treated as adverse events.

7.4.3 Follow-Up

If adverse events or clinically significant abnormalities in examination values are found, if the subject becomes pregnant, or if abnormalities are found in subjective symptoms/objective findings, the principal investigator or sub-investigator will perform the appropriate examination or inspection, even after the completion or discontinuation of the trial, to assure the safety of the subject.

Follow-up is carried out, as a general rule, even if the subjects recover from the adverse event or return to their status before administration. The examination items on the day of occurrence (the day abnormal variations in examination items are found), degree (severity), study drug administration status, any intervention performed to alleviate the adverse event (excluding changes in dosage or discontinuation of treatment with the study drug), outcome (day of the resolution of the adverse event), and the degree of causal relationship with the study drug (four stages) will be recorded in the case report. Furthermore, decision rationale, treatment details, elapsed time, other comments, among others, will be recorded in detail in the medical record. For clinical test items not specified in the trial protocol, in addition to the abovementioned details, measurement values at the time of assessment and/or any alternative data will be recorded.

If there are adverse events, follow-up will be conducted until their resolution or until the outcome is clear, and the laboratory test values with abnormal variations will be measured until the values stabilize.

7.5 Other Evaluation Items

- Hemoglobin A_1c value
- Mitochondrial gene mutation rate of blood leukocytes, $tRNA^{Leu(UUR)}$ taurine modification rate, and NADH dehydrogenase 6 protein mass

・ MMSE score

7.6 Concomitant Drugs and Treatments

From 4 weeks before consent is obtained until the end of the observation period or until discontinuation, details, concomitance period, and reason for concomitance will be surveyed and recorded in the case report for all drugs and treatments in use. For L-arginine, the dose of oral L-arginine used before consent is obtained (26 weeks or more, up to 78 weeks) will also be recorded.

8. Obtaining Informed Consent and Providing Information to Subjects

8.1 Procedures for Obtaining Informed Consent

The principal investigator will create explanatory documents and a consent form (hereafter, called consent/explanatory documents) as well as explanatory documents for underage patients and an assent document (hereafter called assent/explanatory documents). Consent/explanatory documents and assent/explanatory documents will be put into one integrated and complete document, which will be revised if necessary. This document will be submitted at length to the medical institution(s) where the trial will be conducted, and approval from the institutional review board (IRB) will be received before the clinical trial begins.

Before subjects participate in the trial, the principal (sub) investigator will fully explain the details using the consent/explanatory documents and—after confirming that the subjects satisfactorily understand—consent for participation will be obtained in writing.

In cases where subjects are underage or obtaining consent from the subjects themselves is difficult, consent will be obtained from a legal guardian. Even in these cases, details will be fully explained using the consent/explanatory documents, and consent for participation in the

clinical trial will be obtained in writing. In this event, records relating to consent and the relationship between the legal guardian and the subject will be recorded. Additionally, if subjects recover to a state where giving consent is possible during the trial, the principal (sub) investigator will once again conduct an explanation of consent and obtain written consent from the subjects themselves.

For underage subjects who are middle school-aged and older, assent will be obtained in writing. For underage subjects over the age of seven who are not yet in middle school, obtaining assent in writing will be attempted as appropriate. However, in cases where a signature cannot be obtained from the subject or in cases where assent is obtained orally but not in writing, a legal guardian will sign the consent form, and it will be noted in the records that assent is acquired from the subject. Legal guardians are always required to provide written consent after assent is obtained from the subject.

8.2 Matters Explained for Consent

The principal (sub) investigator will explain the details of the clinical trial to subjects and/or legal guardians using explanatory documents that include the following matters:

(1) The clinical trial is in accordance with research.

(2) The objective of the clinical trial.

(3) The name, title, and contact information of the principal and sub investigators.

(4) The method for the clinical trial (the trial’s testing aspects and subject selection criteria).

(5) The expected clinical benefits as well as risks and inconveniences.

(6) If a patient becomes a subject, other treatment methods available for that subject and the expected significant risks and benefits.

(7) The expected length of participation of the subject in the clinical trial.

(8) The subject's participation in the trial is voluntary, and the subject or their legal guardian can refuse or withdraw the subject from the trial at any time. In addition, the subject will not be treated unfavorably because of refusal/withdrawal and will not lose benefits that they should have received because they did not participate.

(9) Monitors, auditors, IRB, among others, as well as the regulatory authorities will be able to view the original documents pertaining to medical care. At that time, subject privacy will be protected. Additionally, subjects and/or legal guardians will be allowed to view the documents with their seal or signature on the consent form.

(10) Subject privacy will be protected even in the event that the clinical trial results are published.

(11) Consultation services at the medical institution where the trial will be implemented that should be referenced to or contacted if subjects wish to obtain further information relating to subject and clinical trial rights or if adverse health events related to the clinical trial occur.

(12) Compensation and treatment that can be provided to the subject if adverse health events related to the clinical trial develop.

(13) The type of IRB that will examine and discuss the appropriateness of this clinical trial, and matters that will be discussed specifically for this study that are not examined and discussed by all IRBs.

(14) The expected number of subjects participating in the trial.

(15) If information that can possibly influence the intention of the subject or their legal guardian to continue participating in the trial is obtained, it will be promptly conveyed to the subject or their legal guardian.

(16) Conditions and reasons for the discontinuation of participation in the trial.

(17) Details in the event that a cost to subjects is necessary.

(18) Details in the event that compensation (e.g., monetary payment) is made to the subject (arrangements for payment calculation).

(19) Conditions subjects must abide by.

8.3 Management of Consent/Explanatory Documents

After the investigator who explains the details signs or seals and dates the consent and/or assent form, a copy of this, along with the explanatory documents, will be hand-delivered to the subject/legal guardian, and the originals will be affixed to the medical records. When personnel collaborating with the trial provide supplementary explanations, that individual's seal or signature and the date will be recorded. Additionally, in the case of electronic charts, after the documents are incorporated electronically, the originals will be stored. For subjects for whom informed consent is obtained, the principal investigator will record the date on which consent is obtained, such as the subject code, and create a "subject identification code list."

8.4 Communication of Information and Revisions to Informed Consent and Explanatory Documents

In the event that new information is obtained that can possibly influence the intention of the subject or their legal guardian to continue participating in the trial, the principal (sub) investigator will convey that information promptly to the subject/legal guardian, confirm whether the subject/legal guardian intends for the subject to continue participation in the clinical trial, and record that information.

Additionally, if consent/explanatory documents and assent/explanatory documents are modified based on that information and approval from the IRB of each medical institution, the principal (sub) investigator will once again provide an explanation using the modified

consent/explanatory documents and/or assent/explanatory documents for the already participating subject and/or their legal guardian and, depending on whether they intend to continue participation, obtain written consent/assent (particulars are the same as those for obtaining consent for the first time).

9. Ensuring Subject Safety

9.1 Basics

Throughout the participation of subjects in the trial, the principal (sub) investigator will conduct necessary and appropriate observations and examinations to ensure subject safety. In case of adverse events, appropriate measures will be taken as necessary, and the cause will be investigated with attention to insurance of patient safety.

9.2 Dealing with Adverse Events

9.2.1 Definition of Adverse Events

Adverse events are any unfavorable medical events (including abnormal laboratory test values) occurring with the administration of the study drug, with no regard to their potential causal relationship with the administration of the study drug. Adverse events occurring until 28 days after the completion of the study drug administration will be included.

However, the following events and abnormal laboratory values, considered to be due to an underlying disease, will not be treated as adverse events.

[Events]

- Stroke-like episodes
- Status epilepticus

- Muscle weakness, fatigability, ataxia, sensorineural hearing loss, myoclonus, hypertrophic cardiomyopathy, heart block, and exacerbation of diabetes mellitus

[Abnormal Lab Values]

Biochemical examination: glucose and HbA_1c levels

Blood tests: blood lactate (deproteinized) and blood pyruvic acid (deproteinized) levels

CSF tests: CSF lactate (deproteinized) and CSF pyruvic acid (deproteinized) levels

Blood leukocyte tests: mitochondrial gene mutation rate, $tRNA^{Leu(UUR)}$ taurine modification rate, and NADH dehydrogenase 6 protein mass.

Additionally, in the event that an adverse event occurs, follow-up will be conducted until that subject has recovered or returned to their state before the administration of the study drug. When subjects have either recovered or recovered with after-effects as a result of adverse events—in cases other than death—the reason will be noted in the medical chart when follow-up is determined to be no longer necessary.

9.2.2 Identifying Adverse Events

For all adverse events, the principal (sub) investigator will identify and record the day of appearance, day of disappearance, degree of severity (serious/not serious), presence or absence of treatment, outcome, action taken with the study drug, and causal relationship with the study drug in the case report.

9.2.3 Definition and Reporting of Serious Adverse Events

Serious adverse events are the adverse events listed below:

(1) Death

(2) Events that may lead to death

(3) Admission to a hospital or clinic for treatment, or extension of hospitalization (hospitalizations for examinations excluded)

(4) Impairment

(5) Events that may lead to impairment

(6) Serious conditions resulting from (1) to (5)

(7) Congenital diseases or abnormalities in future generations

When a serious adverse event appears, the principal (sub) investigator will fill in the necessary items of the "Serious Adverse Event Report" and report directly to the head of the medical institution where the trial is being conducted. They will also inform the coordinating investigator and the study drug provider of the appearance of the serious adverse event. The coordinating investigator will confirm the details of the adverse event report—received from the principal investigator—and notify the principal investigators at other participating medical facilities of that adverse event report.

Procedures for managing safety reports will be created separately in accordance with the "Safety Report Management Procedures."

9.2.4 Causal Relationship with the Study Drug

Causal relationships with the study drug will be identified in accordance with the criteria in the table below.

Table 4. Causal Relationship Identification Criteria

Classification	Criteria

1. Clearly related	When there is an obvious temporal correlation (including the course after administration is discontinued), and the situation corresponds to any of the following: if the same findings are coincident with additional administration, a positive result on drug sensitivity testing (e.g. lymphocyte culture, skin test), or a toxic level of the study drug in bodily fluids (e.g. blood).
2. Probably related	When there is an obvious temporal correlation (including the course after administration is discontinued), and factors other than the study drug, such as underlying disease, complications, concomitant drugs, and concomitant treatments, can, for the most part, be ruled out.
3. The absence of relationship cannot be conclusively established	When there is an obvious temporal correlation (including the course after administration is discontinued), and other factors such as underlying disease, complications, concomitant drugs, and concomitant treatments can, for the most part, be ruled out. However, the possibility that the adverse event results from the study drug cannot be excluded (for example, events where there are reports of the same event in the past for analogous compounds, events inferred from pharmacological action)
4. No relation	When there is no temporal correlation or the event can be clearly explained as due to other factors such as an underlying disease, complications, concomitant drugs, or concomitant treatments.

9.2.5 Extent of Adverse Events (Severity)

The extent of adverse events will be identified in accordance with the criteria in the table below.

Table 5. Adverse Event Severity Identification Criteria

	Criteria
1. Mild	To the extent that adverse event(s) do not affect the subject's daily life. The subject is able to continue administration of the study drug without treatment for associated symptoms or any change to the study drug dosage, etc.
2. Moderate	To the extent that the adverse even(s) cause some impediment to the subject's daily life. The subject requires treatment for associated symptoms, or changes in dose, suspension, or discontinuation of the study drug (excluding discontinuation due to patient request).
3. Severe	To the extent that the tasks of daily life are impossible for the subject. There is no choice but to provide treatment for adverse event(s), in addition to discontinuation of administration of the study drug (excluding discontinuation due to patient request).

9.2.6 Definition of Side Effects

Adverse events for which a causal relationship with the study drug cannot be denied (1. Clearly related, 2. Probably related, and 3. The absence of relationship cannot be conclusively established) will be treated as side effects.

Unpredictable side effects are those that are not recorded in the study drug overview documents, or those for which, though they are recorded, the nature and severity do not conform to the recorded contents.

9.3 Expected Side Effects of the Study Drug

The expected side effects of the study drug are as follows (based on the pharmaceutical product insert provided for 98% Taurine “Taisho” [2007]):

Thirty-eight incidences of side effects were seen in 30 (2.82%) of a total of 1,064 cases. The main side effects for the digestive system were as follows: nausea in 5 (0.47%), diarrhea in 4 (0.38%), abdominal discomfort in 4 (0.38%), constipation in 3 (0.28%), loose stools in 3 (0.28%), loss of appetite in 3 (0.28%), exacerbation of peptic ulcer in 1 (0.09%), and unspecified in 5 (0.47%) cases. Other side effects were hypersensitivity (4 cases with rash, 0.38%), full body symptoms (2 cases with fatigue, 0.19%; 1 case with fever incident, 0.09%), neuropsychiatric alterations (1 case with drowsiness, 0.09%; 1 case with euphoria, 0.09%), and central nervous system alterations (1 case with headache, 0.09%) [at the end of reevaluation].

10. Discontinuation Criteria and Procedures for Each Subject

10.1 Discontinuation Criteria

The trial will be discontinued in following conditions: (If the trial is discontinued, the reason will be determined and recorded in the case report; additionally, the specified examinations will be implemented to the fullest extent possible at the time of discontinuation.)

(1) If the subject or legal guardian withdraws consent.

(2) If the subject or legal guardian requests a change or discontinuation of treatment.

(3) If the principal (sub) investigator determines that continuation in the trial is inappropriate because of adverse events (e.g., worsening of complications or diagnosis of a new disease).

(4) If the principal (sub) investigator determines that continuation in the trial is not reasonable because of a worsening of the underlying disease.

(5) If the subject's place of residence changes, etc. and the subject is no longer able to visit the predetermined hospital.

(6) If the subject becomes pregnant.

(7) If the subject is found to be incompatible with the selection criteria or to violate the exclusion criteria.

(8) If a serious deviation from the clinical trial protocol is found.

(9) If the principal (sub) investigator determines that continuation in the trial is not appropriate for other reasons.

10.2 Discontinuation Procedures

If the trial is discontinued because of a safety issue, such as adverse events or worsening of the underlying disease/complications, the principal (sub) investigator will promptly take appropriate action, conduct the necessary examinations to the full extent as possible after discontinuation, and record parameters such as the day of discontinuation, reason and circumstances that led to the discontinuation, and the treatment implemented in the case report. Additionally, the progression will be observed until follow-up is determined to be no longer necessary.

11. Statistical Analysis

11.1 Statistical Considerations

The main statistical items for this clinical trial are detailed in the following sections. (Details will be separately included in the “Statistical Analysis Protocol.”)

11.2 Efficacy Evaluation

11.2.1 Demographics and Other Baseline Values

This will provide an overview of subjects as well as summary statistics for demographic variables (e.g. gender and age), disease factors (e.g. complications and medical history), and other potentially related factors.

11.2.2 Analysis Set for Efficacy Evaluation

The primary analysis set for this clinical trial, the Full Analysis Set (FAS), will consist of all subjects registered in the trial, excluding those for whom the following is applicable:

- Subjects with serious departures from good clinical practice (GCP)
- Subjects for whom the study drug is not administered even once
- Subjects for whom efficacy evaluations are never conducted

Additionally, subjects for whom the following criteria are applicable will be excluded from the FAS to create the Per Protocol Set (PPS, analyses using the PPS will be conducted to confirm the robustness of the results of analyses using FAS):

- Subjects who do not meet the selection criteria or those who violate the exclusion criteria
- Subjects for whom the study drug administration period was less than 26 weeks
- Subjects for whom the study drug administration rate was less than 70%.

Efficacy in this clinical trial will be evaluated with the total cases using FAS and PPS.

Further evaluation will be performed with no L-arginine Co-Administration and L-arginine Co-Administration cases separately.

Furthermore, as subjects suitable for a more appropriate evaluation of the efficacy of this drug, main analyses will also be conducted using the following subjects from FAS/PPS:

- Subjects in which at least two stroke-like episodes are confirmed in the 78-week period before consent is obtained (i.e., those meeting the MELAS stroke diagnostic criteria).
- Secondary evaluations will also be conducted with the following patients:
- Subjects in whom focal neurological signs (with no consideration of high-intensity signals detected by brain MRI) are confirmed at least two times in the 78-week period before consent is obtained and those in whom focal neurological signs are confirmed at least once with the presence of high-intensity lesion(s) using diffusion-weighted brain MRI.
- Subjects in whom focal neurological signs (with no consideration of high-intensity lesion(s) observed with diffusion-weighted brain MRI) are confirmed at least two times in the 78-week period before consent is obtained.
- Subjects in whom at least two stroke-like episodes meeting the MELAS stroke diagnostic criteria are confirmed in the 52-week period before consent is obtained.
- Subjects in whom focal neurological signs (with no consideration of high-intensity lesion(s) observed with diffusion-weighted brain MRI) are confirmed at least two times in the 52-week period before consent is obtained.

11.2.3 Efficacy Endpoint Analysis Method

(1) Primary Endpoint Analysis Method

Primary analysis: Based on the Clopper-Pearson method, an exact 95% confidence interval will be

assumed. Secondary analysis: The effect of the study drug and background parameters on the percentage of 100% responders will be evaluated using logistic regression analysis. A confidence interval of 95% for the 100% responder rate based on the Clopper-Pearson method will be assumed for the total cases. It will be further assumed for no L-arginine Co-Administration and L-arginine Co-Administration cases separately.

(2) Secondary Endpoint Analysis Method

An exact 95% confidence interval will be assumed based on the Clopper-Pearson method for the 50% responder rate. The effect of the study drug and background parameters on the percentage of 100% responder rate will be evaluated using logistic regression analysis. An exact 95% confidence interval based on the will be assumed for the total cases. It will be further assumed for no L-arginine Co-Administration and L-arginine Co-Administration cases separately.

For each measurement point, summary statistics will be calculated for clinical symptoms (mitochondrial disease severity score), blood and CSF taurine, lactate, and pyruvic acid levels, and lactate/pyruvic acid ratio. Summary statistics will be calculated for before and after the clinical trial for the number of abrupt-onset focal neurological deficits (not regarding confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI) observed, number of times intravenous arginine is used before and after the study drug administration, and number of times high-intensity lesion(s) are confirmed with diffusion-weighted brain MRI based on the appearance of headaches, nausea/vomiting, convulsions, and/or impaired consciousness.

Additionally, time, study drug, time and study drug interaction, and other background parameters will be evaluated for their association with changes in each parameter over time as necessary, using a marginal or mixed model.

11.3 Safety Evaluation

11.3.1 Analysis Set for Safety Evaluation

Analyses will be conducted with the group of registered subjects for whom the study drug has been administered at least once. This includes subjects who experience adverse events and those who are later determined to have violated the exclusion criteria after study drug administration.

11.3.2 Safety Endpoint and Analysis Method

Incidence for all and individual adverse events and side effects that are observed in this clinical trial.

12. Clinical Trial Method

12.1 Registration of Subjects

Subjects will be registered by the central registration method.

(1) For subjects that meet the selection criteria and do not violate the exclusion criteria, the principal (sub) investigator will explain the details of the clinical trial using the consent/explanatory documents and request participation, and subjects who give consent will be registered.

(2) Registration will be conducted by entering the necessary items into the electronic data capture (EDC) system. After registration, a subject identification code will be automatically assigned.

(3) The principal (sub) investigator will begin administration of the study drug for subjects determined to be eligible.

(4) The principal (sub) investigator will enter and save the automatically assigned subject identification code to the “Subject Identification Code List.”

12.2 Discontinuation or Interruption of a Trial

12.2.1 Criteria for Discontinuation or Interruption of a Trial

In the event of any of the following, determined by either the coordinating investigator or those implementing the trial independently from the medical institutions, whether or not the clinical trial should be continued in its entirety or at one medical facility will be investigated:

(1) If information on the quality of the study drug, items relating to its efficacy or safety, or other critical information relevant for the suitability of the clinical trial is learned.

(2) If modifications to the clinical trial protocol are required, and the medical institution(s) at which the trial is being implemented cannot provide support the trial.

(3) If there is a modification of the instructions in the clinical trial protocol, etc. from the director of the medical institution at which it is being implemented based on the opinion of the IRB, and the coordinating investigator or those participating in the trial independently cannot agree to it.

(4) If the director of the medical institution(s) at which the trial is being implemented instructs the discontinuation of the trial based on the decision of the IRB.

(5) If the medical institution at which the trial is being implemented conducts a serious or continuing breach of GCP or the clinical trial protocol. The principal investigator of each institution will promptly report to the coordinating investigator if the trial at their facility is discontinued. Additionally, if this trial is discontinued or interrupted, it will be promptly reported to the coordinating investigator and explained in detail.

12.2.2 Discontinuation or Interruption of the Entire Trial

If the coordinating investigator or an individual conducting the trial independently decides to discontinue or interrupt the entire trial, the director of the medical facility at which the trial

is being implemented and the regulatory authority will be promptly informed of this decision, with disclosure of the reason in writing. If the director of the institution at which the trial is being implemented receives this notice from the coordinating investigator or individual conducting the trial independently, they will promptly inform the IRB of this decision, with disclosure of the details.

If the clinical trial is interrupted or discontinued, the principal investigator will promptly inform the subjects and ensure that they receive proper treatment.

Correspondence with subjects in the event of the clinical trial discontinuation will be conducted in accordance with the “Discontinuation Procedures” in Section 10.2

12.2.3 Discontinuation or Interruption of a Trial at a Medical Institution by the Institutional Review Board

If the IRB decides to interrupt or discontinue the clinical trial, the director of the medical institution at which the trial is being implemented will be promptly informed of this in writing, including the details of the reason(s). The director of the medical institution will promptly inform the principal investigator and coordinating investigator of this in writing.

13. Case Reports

13.1 Format of Case Reports

In this clinical trial, an electronic case report utilizing an EDC system will be used. An electronic case report, for which the contents are confirmed and electronically signed by the principal investigator, will be treated as the original. CD-Rs from the electronic case reports at the institutions implementing the trial will be created, copied, and stored. (The electronic case file that is electronically signed by the principal investigator will be saved as a PDF).

13.2 Material Entered Directly into the Case Report and Materials that Should Be Used as Original Data

Of the data entered into the case report, the following items will be used as original data:

(1) Purpose of concomitant drugs and purpose of concomitant treatments

(2) Adverse events (severity, degree, outcome, day of outcome, and reason for classifying a causal relationship with the study drug)

(3) Day of discontinuation, reason for discontinuation, adverse event that caused the discontinuation, progression, and follow-up results after discontinuation

(4) Principal (sub) investigator comments.

13.3 Notes on Case Report Writing

Case reports will be created by the principal (sub) investigator or personnel collaborating with the trial, according to the following specifications:

(1) Prior to entering information into the case report, an individual in charge of data management will issue the principal (sub) investigator/collaborating personnel with a user ID and password and will manage users. Each individual who receives a username and password will manage only that account. Accounts will not be shared.

(2) Case reports will be created for subjects to whom the study drug is administered.

(3) Data input will be conducted by those with input privileges—the principal (sub) investigators and collaborating personnel. Principal investigators will be able to work on every item of the case report. Sub-investigators will be able to work on every item of the case report other than the electronic signature. Coordinating personnel will be able to

transcribe from other sources such as the medical records and transcribe items not involving medical decisions from the original sources.

(4) In the event of changes or corrections to the case report, the reason for the change or correction will be recorded electronically.

(5) After confirming the accuracy and integrity of the case report, with reference to the audit history and electronic signature information, the principal investigator will electronically sign the case report form in the EDC system.

(6) The principal investigator will take custody of a copy (the electronic case report with the contents confirmed by the principal investigator saved as a PDF) of the saved (CD-R, etc.) case report form. After it is electronically signed, for the period before a CD-R, etc. is provided, the individual in charge of data management will substitute it with a duplicate through the provision of a browsing environment (EDC system access privileges).

(7) If there is any contradiction with the original source in the data recorded in the case report, the principal investigator will create a record explaining the reason, submit it to the individual in charge of data management, and save a copy.

14. Compliance with Ethical Principles

This clinical trial will be implemented in compliance with the ethical principles of the Declaration of Helsinki, pharmaceutical affairs law, and GCP, in addition to this clinical trial protocol.

15. Institutional Review

15.1 Approval of the Institutional Review Board

Before this clinical trial is conducted, the IRBs of the medical institutions at which the trial will be implemented will examine and approve the clinical trial protocol, the details of the information in the consent/explanatory documents for subjects, and the appropriateness of the trial from the standpoints of ethical, scientific, and medical validity.

15.2 Review for Trial Continuation

For the purpose of continuing the clinical trial, the principal investigator will report to the IRB once per year regarding the status of the clinical trial, and the continuation of the trial will be subject to review.

Additionally, if information is obtained that will necessitate a secondary IRB investigation related to the continuation of the trial, or if a serious modification to the clinical trial protocol is made, it will be reported to the IRB, and the continuation of the trial will be subject to review.

16. Trial Protocol Compliance, Deviation, Change, and Revision

16.1 Compliance with Trial Protocol

The principal (sub) investigator will implement the clinical trial in compliance with this clinical trial protocol.

16.2 Deviations from and Changes to Trial Protocol

Principal (sub) investigators cannot deviate from or change the clinical trial protocol without obtaining prior written approval based on a review from the IRB. However, deviation from, or changes to, the clinical trial protocol without prior approval from the IRB will be allowed in circumstances where there is medically no other choice, such as the

presence of an urgent risk to the subjects. In that case, if the deviation or modification details and reasoning as well as the amendments to the trial protocol are appropriate, the principal investigator will submit a draft to the director of the medical institution and the IRB as quickly as possible. IRB approval, written acknowledgement from the director of the medical institution, and approval from the coordinating investigator will be required.

Principal (sub) investigators will be required to record all conduct that deviates from the clinical trial protocol. The principal investigator will be required to submit a written record of the rationale directly to the director of the medical institution and the coordinating investigator and save a copy only if a deviation from the clinical trial protocol is implemented when there is medically no other choice, such as to the presence of urgent risk to the subjects.

If any changes to the clinical trial will seriously influence the implementation of the trial or increase risk to the subjects, the principal investigator will submit a written report promptly to the director of the medical institution, the IRB, and the coordinating investigator.

16.3 Revisions to Trial Protocol

If a modification to the trial protocol is found to be necessary during the trial by the coordinating investigator or those independently conducting the trial, the trial protocol will be revised. The coordinating investigator or those independently conducting the trial will promptly inform the director of the medical institution of the details of the revision in writing, and approval from the IRB will be obtained by the director of the medical institution.

If the director of the medical institution is instructed to modify the trial protocol based on the opinion of the IRB, the coordinating investigator and/or those independently conducting the trial will revise the trial protocol as necessary. The director of the medical institution will

be promptly informed of the details of the revision in writing, and approval from the IRB will be obtained by the director of the medical institution.

16.4 Provision of New Information

If the coordinating investigator or those conducting the trial independently obtain information indicating that the study drug will have a negative effect on the safety of the subject, information that can influence the implementation of the trial, or information that will necessitate a secondary investigation related to the continuation of the trial by the IRB, the director of the medical institution will be promptly informed in writing.

If new information that is necessary to convey to the subjects is obtained, those conducting the trial independently will modify the consent/explanatory documents promptly and obtain approval from the IRB.

17. Direct Access to Trial Material

The principal investigator or the director of the institution assures that upon receiving an inquiry from those monitoring the coordinating investigator or those independently conducting the trial, auditors, the IRB, or regulatory authorities, they will be guaranteed direct access to all materials relating to the trial.

18. Quality Control and Quality Assurance of the Trial

The coordinating investigator and/or those conducting the trial independently must conduct quality control and quality assurance for the purpose of maintaining the quality and reliability of the trial. Additionally, the medical institution(s) must cooperate in trial quality control and quality assurance, according to the coordinating investigator and/or those independently conducting the trial.

For quality control of the trial, source materials will be directly monitored, and procedural documents relating to trial operations at the medical institutions and compliance with the latest trial protocols and GCP will be confirmed as appropriate. Additionally, the accuracy and integrity of the details of case reports prepared by the principal (sub) investigator will be ensured with reference to the source material, including trial-related records.

Additionally, audits will be performed by those in charge in accordance with the procedural manual that will confirm that appropriate quality control measures are practiced to guarantee that the trial is being conducted in compliance with the clinical trial protocol and GCP.

19. Costs Related to Trial Participation

Expenses related to drugs other than the study drug during the clinical trial period or medical care other than the specified examination items will be fall under medical insurance. Expenses for trial collaboration will be paid in accordance with the specifications of each medical institution. The study drug used in this clinical trial will be supplied by the provider free of charge.

20. Compensation for Injury

In the event of injury to the subject, the medical institution implementing the trial will provide the necessary support such as medical care and perform the necessary and appropriate treatment. At that time, if the injury occurs from the appropriate use of the study drug, and the principal investigator identifies a causal relationship with the study drug, the burden of the compensation costs will fall on the principal investigator. If the injury is determined to be due to the injured subject’s deliberate or gross negligence, they may not be eligible for compensation.

In observance of the contract measures, in the event that liability arises because of an injury resulting from the clinical trial, the coordinating investigator will provide insurance for the coordinating investigator, principal investigator, sub investigator, and the medical institution. Additionally, the principal investigator and sub investigator will have physician liability insurance, and the medical institutions will have hospital liability insurance.

21. Record Keeping

21.1 Storage of Records for Trials at Medical Institutions

The record keeper appointed by the head of the medical facility will save the necessary documents and records relating to the trial for the medical facility until a later date, as specified in (1) or (2) below. However, if the coordinating investigator, or those implementing the study independently from any of the medical institutions, sees it necessary to save them for a longer period, the medical facility will discuss the preservation period and method with the coordinating investigator/those independently implementing the study.

Additionally, in the event that the provider of the study drug decides not to approve request form, the head of the medical facility will be informed of this and the reason in writing.

1) The manufacturing and marketing approval date for the study drug (alternatively, the discontinuation of development, or three years past the day notice is received that the clinical trial results will not be sent with the approval request form).
2) Three years past the day that the clinical trial is discontinued or completed.

If the study drug provider receives manufacturing and marketing approval, or if approval is not received and the development is discontinued, this will be reported to the head of the medical facility in writing.

21.2 Storage of Records for Those Conducting the Trial on Their Own

Those carrying out the trial on their own will save the necessary documents and records relating to their trial until a later date as specified in 1) or 2) below. The study drug provider will be consulted for correspondence after the end of the storage period.

(1) The manufacturing and marketing approval date for the study drug (alternatively, the discontinuation of development, or if notice is received that the clinical trial results will not be sent with the approval request form and development is discontinued, or three years past the day notice is received that they will not be sent with the request form).

(2) Three years past the day that the clinical trial is discontinued or completed.

If the study drug provider receives manufacturing and marketing approval, or if approval is not received and the development is discontinued, this will be reported to the head of the medical facility in writing.

22. Protection of Confidentiality and Personal Information

Subject registration and case reports will be created with subject-specific subject identification codes and protection of personal information in such a way that subjects cannot be identified and will be given full consideration for direct access to raw data relating to the trial, subject consent forms, etc. and the publication of the research results. Personal information obtained from subjects for this clinical trial will not be disclosed to third parties.

23. Publication and Attribution of the Clinical Trial Results

The information (data, etc.) from this clinical trial, or any portion thereof, cannot be published by any method without prior permission of the coordinating investigator, those participating in the trial independently, and the study drug provider.

24. Trial Organization

24.1 Coordinating Investigator

Responsible for the management and supervision of this clinical trial:

Professor Sunada Yoshihide

Kawasaki Medical School, Department of Neurology

TEL: 086-462-1111 (Ext. 27507)

FAX: 086-464-1027

24.2 Coordinating Executive Officer

Coordination of operations for management of this clinical trial:

Professor Sunada Yoshihide

Kawasaki Medical School, Department of Neurology

TEL: 086-462-1111 (Ext. 27507)

FAX: 086-464-1027

24.3 Trials Conducted at Medical Institutions and by Individual Principal Investigators

See KN01 Study Investigators in the supplementary appendix.

24.4 Study Drug Provider

Taisho Pharmaceutical Co., Ltd. (Tokyo, Japan) provided good manufacturing practice-grade taurine.

24.5 Development of Outsourcing Institution and Laboratory

See attached sheet (Attachment 1).

24.6 Trial Costs

This clinical trial will be conducted through the Health, Labor, and Welfare Grant-in-Aid for Scientific Research: Overcoming Intractable Diseases Research Program (H24-Nanchitou(Nan)-Ippan-068).

25. References

1) Yasukawa T, Suzuki T, Suzuki T, et al. Modification defect at anticodon wobble nucleotide of mitochondrial tRNAsLeu(UUR) with pathogenic mutations of mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes. J Biol Chem 2000;275:4251-7

2) Yasukawa T, Suzuki T, Ishii N, et al. Wobble modification defect in tRNA disturbs codon-anticodon interaction in a mitochondrial disease. EMBO J 2001;20:4794-802

3) Rikimaru M, Ohsawa Y, Wolf AM, et al. Taurine ameliorates impaired the mitochondrial function and prevents stroke-like episodes in patients with MELAS. Int Med 2012;3351-7

4) Yatsuga S, Povalko N, Nishioka J, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Act 2012;1820:619-24

5) Davidson MM, Walker WF, Hernandez-Rosa E. The m.3243A>G mtDNA mutation is pathogenic in an in vitro model of the human blood brain barrier. Mitochondrion 2009;9:463-70

6) Kamata T, Koizumu T, Kozima J, et al. A double-blind, placebo-controlled clinical evaluation of taurine in acute hepatitis. Sulfur Amino Acids 1980;3:223-35 (in Japanese)

7) Matsuzaki Y, Tanaka N, Osuga T. Is taurine effective for treatment of painful muscle cramps in liver cirrhosis? Am J Gastroenterol 1993;88:1466-7

8) Nomoto M, Izumi K, Tominaga H, et al. Efficacy of taurine in tardive dyskinesia and essential tremor. Sulfur Amino Acids, 1983;6:47-51

Attachment 1. Date of Creatioin: 10/2/2013

24.3 Site Institutions and Clinical Trial Implementing Parties (Investigators)

24.3.1 Site Institutions and Clinical Trial Implementing Parties (Investigators)

Kawasaki Medical School Hospital, Neurology, Yoshihide Sunada (Department Director), 577 Matsushima, Kurashiki-shi, Okayama-ken, 701-0192, Japan, Phone: 086-462-1111

National Defense Medical College Hospital, Division of Neurology, Anti-aging, and Vascular Medicine, Hiroyuki Onoue (Appointed Lecturer), 3-2 Namiki, Tokorozawa-shi, Saitama-ken 359-8513, Japan, Phone: 04-2995-1511

Seirei Hamamatsu General Hospital, Neurology, Tsuyoshi Uchiyama (Department Director), 2-12-22 Sumiyoshi, Naka-ku, Hamamatsu-shi, Shizuoku-ken, 430-8558, Japan, Phone: 053-474-2222

Fujita Health University Hospital, Neurosurgery Department, Prof. Tatsuro Mutoh

1-98 Dengakugakubo, Kutsukake-cho, Toyoake-shi, Aichi-ken 470-1192, Japan, Phone: 0562-93-2111

National Hospital Organization Kyoto Medical Center, Internal Medicine of Neurology, Michikazu Nakamura (Head Physician), 1-1 Mukaihata-cho, Fukakusa, Fushimi-ku, Kyoto-shi, Kyoto-fu, 612-8555, Japan, Phone: 075-641-9161

Hyogo-Chuo National Hospital, Internal Medicine of Neurology, Katsuya Nishida

1314 Ohara, Sanda-shi, Hyogo-ken, 669-1592, Japan,Phone: 079-563-2121

Fukuoka University Chikushi Hospital, Department of Pediatrics, Prof. Atsushi Ogawa, 1-1-1 Zokumyoin, Chikushino-shi, Fukuoka-ken, 818-8502, Japan, Phone: 092-921-1011

Kurume University, Medical School Hospital, Department of Pediatrics, Prof. Yasutoshi Koga, 67 Asahi-machi, Kurume-shi, Fukuoka-ken, 830-0011, Japan, Phone: 0942-35-3311

Nagasaki University Hospital, Internal Medicine of Neurology, Hirokazu Shiraishi

1-7-1 Sakamoto, Nagasaki-shi, Nagasaki-ken, 852-8501, Japan, Phone: 095-819-7200

Hiroshima University Hospital, Department of Neurology, Associate Professor of Medical Treatment, Tetsuya Takahashi, 1-2-3 Kasumi, Minami-ku, Hiroshima-shi, Hiroshima-ken, 734-8551, Japan, Phone: 082-257-5555

[Main Tasks]

As the lead party responsible for the team of subinvestigators, trial collaborators and other members, the investigators are charged with managing and directing as well as heading the tasks related to this clinical trial at the site institutions.

24.3.2 Research Organization

Kawasaki Medical School, Department of Neurology, Prof. Yoshihide Sunada

[Research duties that are shared] Support for conclusions and serious adverse events

Kawasaki Medical School, Department of Neurology, Yutaka Osawa (Lecturer)

[Research duties that are shared] Support for data management

Kawasaki Medical School, Department of Neurology, Assoc. Prof. Tatsufumi Murakami

[Research duties that are shared] Support for personal information

Teikyo University of Science, Faculty of Medicine, Prof. Hiroki Hagiwara

[Research duties that are shared] Support for monitoring and authorities

National Center of Neurology and Psychiatry, Department of Mental Retardation and Birth Defect Research, Yuichi Gotoh (Department Director)

[Research duties that are shared] Support for registry

Kurume University, Medical School Hospital, Department of Pediatrics, Prof. Yasutoshi Koga [Research duties that are shared] Support for monitoring and auditing

Kawasaki Medical School, Molecular Biology I (Embryology), Shinichiro Nishimatsu (Lecturer)

[Research duties that are shared] Support for specimens and intellectual properties

Graduate School of Nippon Medical School, Aging Science, Prof. Shigeo Ohta

[Research duties that are shared] Support for specimens and intellectual properties

24.4 Investigational Medicinal Product Suppliers

Taisho Pharmaceutical Co., Ltd.

3-24-1 Takada, Toshima-ku, Tokyo, 103-0024, Japan

Phone: 03-3985-1111

[Main Tasks]

The following duties are carried out based on the consultation with coordinating investigators and investigators.

1) The investigational medicinal product is provided to the investigational product administrator established by the investigators or the directors of the site institutions.
2) Information such as the safety information related to the investigational medicinal product is collected and provided.

24.5 Contract Research Organization and Testing Organization

24.5.1 Contract Research Organization

(1) Project Management

CTD Inc.

3-3-2 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan

Phone: 03-6228-4105 Fax: 03-6228-4843

Responsible party: Fumiaki Kobayashi

Associates in charge: Kazuo Watanabe and Mai Moriyama

[Main Tasks]

The trial coordinating agency provides support based on instructions from the coordinating investigator.

(2) Monitoring

DOT WORLD CO.,LTD.

PMO Hatchobori Building 3-22-13 Hatchobori , Chuo-ku, Tokyo, 104-0032, Japan

Phone: 03-3523-0210　Fax: 03-3523-0225

Responsible Party: Tetsuya Orito

Clinical Research Associates: Namiko Murao,　Keiko Onodera, Naoko Kataoka, Ayumi Kuramoto,　Miho Araki, Hiroko Iijima, Yukihisa Fujisawa, Mariko Shimobayashi, Yuki Yabe

[Main Tasks]

Follow procedures according to separately created documents and conduct monitoring.

(3) Auditing

SRD Co., Ltd.

RBM Kyobashi Building 3-4-8 Hatchobori, Chuo-ku, Tokyo, 104-0032, Japan

Phone: 03-5543-0297　Fax: 03-5543-0184

Responsible Party: Seichi Ooba

Associates in charge: Yuki Shoji, Taka Kubota

[Main Tasks]

An audit is conducted following a procedure that is created separately, in order to check the suitability of the trial system and the reliability of the data for this study.

(4) Data Management

DOT WORLD CO.,LTD.

PMO Hatchobori Building 3-22-13 Hatchobori, Chuo-ku, Tokyo, 104-0032, Japan

Phone: 03-3523-0210　Fax: 03-3523-0225

Responsible Party: Tatsuhiro Uenishi

Associate in charge: Atsushi Koda

Part of these duties is re-contracted to Takumi Information Technology Inc.

[Main Tasks]

1) Preparations for data management (Creating data input screen, creating input manual, creating data management plan, creating code rules, creating check list for data input)

2) Providing feedback for discrepancies in data (logical checks, issuing queries)

3) Coding (Adverse events, concomitant drugs, etc.)

(5) Statistical Analysis

DOT WORLD CO.,LTD.

PMO Hachobori Building 3-22-13 Hachobori, Chuo-ku, Tokyo, Japan, 104-0032

Phone: 03-3523-0210 Fax: 03-3523-0225

Responsible Party: Tatsuhiro Uenishi

Associate in charge: Atsushi Koda

Part of these duties is re-contracted to Takumi Information Technology Inc.

[Main Tasks]

The Statistical Analysis Plan is created following the analysis method noted in the Protocol, and the calculation and analysis is carried out following that plan. However, the duties are discussed and reviewed with the person in charge of data management.

(6) Medical Writing

DOT WORLD CO.,LTD.

PMO Hatchobori Building 3-22-13 Hatchobori, Chuo-ku, Tokyo, 104-0032, Japan

Phone: 03-3523-0210 Fax: 03-3523-0225

Responsible Party: Mayumi Saotome

Associates in charge: Chie Arai, Ryo Yano

[Main Tasks]

Preparation of the Clinical Study Report (Draft).

24.5.2 Testing Organization

(1) Blood WBC: Measurement of $tRNA^{Leu(UUR)}$ taurine modification rate

Kawasaki Medical School, Molecular Biology I

577 Matsushima, Kurashiki-shi, 701-0192, Japan

Phone: 086-462-1111　Ext. 78078

Associates in charge: Shinichiro Nishimatsu

(2) Blood WBC: Measurement of mitochondrial DNA mutation rate, ND6 protein level

Nippon Medical School – Institute of Gerontology, Cell Biology

1-396 Kosugimachi, Nakahara-ku, Kawasaki-shi, Kanagawa-ken, 211-8533, Japan

Phone: 044-733-9267

Associate in charge: Shigeo Ohta

(3) Measurement of lactic acid (in blood and CSF), pyruvic acid (in blood and CSF), amino acid analysis (in blood and CSF)

SRL Medisearch Inc.

Shinjuku I-Land-Tower 10F, 6-5-1, Nishishinjuku, Shinjuku-ku, Tokyo 163-1310, Japan

Phone: 03-5324-2602　Fax: 03-5324-3508

Responsible party: Katsuhiro Ikeoka

Measurement Organization:

SRL Inc.

2-1-1 Nishishinjuku, Shinjuku-ku, Tokyo 163-0409, Japan

Phone: 03-6279-0900

Responsible party: Yoji Hirabayashi

[Main Tasks]

1) Specimens are collected.

2) The specimens are measured.

3) The specimen results report and the coordinating tasks are conducted.

Attachment 2: MELAS Diagnosis Criteria Date of Creation: 6/28/2013

MELAS Diagnosis Criteria was originally created by Koga Group (a Research Grant from the Ministry of Health, Labour and Welfare of Japan, March 2005; Yatsuga S, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Acta 2012;1820:619-24).

◆**Recognition Criteria / Certain Cases**

Cases that meet item 2 in the clinical findings for apoplexy in A. and meet item 2 for the rationale of mitochondria abnormalities below (Minimum of 4 items in total required).

A. Clinical Findings for Apoplexy

1. Headache and vomiting
2. Convulsion
3. Hemiplegia
4. Homonymous hemianopsia or cortical blindness
5. Acute local abnormal finding of the brain in brain image Note 1

B. Rationale for Mitochondrial Abnormality

1. Lactic acid level in blood and CSF is repeatedly high, or absence of mitochondria related enzyme Note 2
2. Malformation of mitochondria in muscle biopsy Note 3
3. (MELAS related) Already known gene mutation Note 4

Note 1. Local brain lesions exist in brain imaging such as head CT or MRI.

Note 2: When lactic acid levels in the blood and pyruvic acid in the CSF while resting in bed is ≥2 mmol/L (18 mg/dL), or when the enzymes are absent in a cell-based (preferably muscular tissue) enzyme search

such as electron transport chain enzymes, pyruvate metabolism related enzymes, TCA cycle related enzymes or lipid metabolism related enzymes.

Note 3: Muscle pathology, such as ragged-red fiber (RRF for Gomori trichrome staining: ragged-red fibers), RRF or SSV (strongly SDH-reactive blood vessels) in succinate dehydrogenase staining or cytochrome-c oxidase deficient fiber, mitochondria morphological defects found using electron microscope, etc.

Note 4: The already known DNA mutations that have been reported as genes that cause MELAS exists (Such as mitochondria tRNA-Leu(UUR) genes A3243G, G3244A, A3252G, A3260G, T3271C and T3291C, and mitochondria tRNA-Val gene G1642A, mitochondria tRNA-Cys gene A5814G, mitochondria COX gene T9957C, mitochondria ND5 gene G13513A mutations)

Attachment 3: The Japanese Mitochondrial Disease Rating Scale (JMDRS)

Date of Creation 12/5/2013

The Japanese Mitochondrial Disease Rating Scale (JMDRS) was originally created by Koga Group (a Research Grant from the Ministry of Health, Labour and Welfare of Japan, March 2005; Yatsuga S, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Acta 2012;1820:619-24). which was modified from the European Neuromuscular Conference mitochondrial disease scale. The European.[Note 1]

Ages that can be assessed: 6 years old and older.

◆Section 1: activities of daily living

A. Speech

0-normal

1-mildly affected, no difficulty being understood

2-moderately affected, may be asked to repeat

3-severely affected, frequently asked to repeat

4-unintelligible most of time

B. Swallowing

0-normal

1-rare choking

2-occasional choking

3-requires soft food

4-requires nasogastric or gastrostomy tube

C. Handwriting

0-normal

1-slightly small or slow

2-all words small but legible

3-severely affected, not all words legible

4-majority illegible

D. Cutting food- handling utensils

0-normal

1-somewhat slow and clumsy but no help needed

2-can cut most foods, some help needed

3-food must be cut, but can feed self

4-needs to be fed

E. Dressing

0-normal

1-somewhat slow and clumsy but no help needed

2-occasional helps with buttons or arms in sleeves

3-considerable help required but can do some things alone

4-helpless

F. Hygiene

0-normal

1-somewhat slow and clumsy but no help needed

2-needs help with shower or bath or very slow in hygienic care

3-requires assistance for washing, brushing teeth, going to bathroom

4-helpless

G. Falling

0-none

1-rare falling

2-less than one per day

3-average of once per day

4-more than one per day

H. Paroxysmal event (migraine, seizures)

0-none

1-<1every1month

2->1every1month<1every week

3->1every1week<1every day

4->1every day/status, Status epilepticus

◆Section 2: motor

A. Proximal muscle strength (modified MRC)

0-normal

1-slight reduction of power (grade4 MRC, MRC4)

2-moderate impairment, able to overcome gravity (MRC3)

3-severe weakness, unable to overcome gravity (MRC2)

4-severe weakness, flicker only (MRC1)

5-no voluntary muscle activity (MRC0)

B. Upper limb coordination

Modified ICARS, International Cooperative Ataxia Rating Scale.

0-normal

1-mild clumsiness- no significant disability

2-moderate clumsiness- poor writing, able to perform ADL

3-severe clumsiness- unable to write

4-severe clumsiness- unable to feed

C. Walking

0-no limitation

1-limited a little (getting tired after 1-2 km)

2-moderately limited (difficulties keeping up with friends)

3-severe limited (having to stop every 100-400m to rest)

4-no walking distance beyond 10m

D. Moderate motor activities

(such as vacuum cleaning, carrying groceries, climbing one flight of stairs , preparing your bed)

0-no limitation

1-limited a little

2-moderately limited

3-severely limited

4-not capable

E. Vigorous motor activities

(such as running, climbing several flights of stairs, or participating on other strenuous sports)

0-no limitation

1-limited a little

2-moderately limited

3-severely limited

4-not capable

◆Section 3: special sensory

A. Vision

0-normal

1-unable to drive or equivalent (i.e. unable to read traffic or shop signs)

2-unable to read normal print books

3-unable to read standard large print books

4-unable to watch TV

5-no useful vision

B. Auditory

0-< 10dB loss

1-0-20 dB loss

2-20-40 dB loss

3-severe >40 dB but improves with hearing aid

4-severe >40 dB loss and does not improve with hearing aid

◆Section 4: endocrine

0-normal

1-single endocrine organ involvement

2-2 endocrine organs involved

3-3 endocrine organs involved

For diabetes, add 1 for insulin treated

◆Section 5: cardiac

0-normal ECG and ECHO

1-conduction system disease, mild impaired LV function (EF >60%)or asymptomatic hypertrophy

2-ECHO evidence of cardiomyopathy and restricted physical activity (EF <60%) or cardiac pacemaker

3-Moderate cardiomyopaty (EF <40-60%)

4-Severe cardiomyopaty

◆Section 6: Renal function[Note 2]

0-Normal

1-Creatinine clearance <50-90 ml/min/1.73 m^2

2-Creatinine clearance 30-50 ml/min/1.73 m^2

3-Creatinine clearance 10-30 ml/min/1.73 m^2

4-Creatinine clearance <10 ml/min/1.73 m^2 or dialysis in needed

◆Section 7: cognition and impairment

A. intellectual impairment

0-normal

1-mild (consistent forgetfulness with partial recollection of events with no other difficulties)

2-moderate memory loss with disorientation and moderate difficulty handing complex problems

3-severe memory loss with disorientation to time and often place, severe impairment with problems

4-severe memory loss with orientation only to person, unable to make judgments or solve problems

B. Motivation and drive

0-normal

1-lacking in energy, does not restrict activities

2-lacking in energy, restricts hobbies and interests

3-lacking in energy, restricts day to day (routine) activities

4-unable to carry out any task

Note 1: In the ENMC (Chinnery PF, Bindoff LA. Europen neuromuscular center. 116th ENMC international workshop: the treatment of mitochondrial disorders, 14th-16th March 2003, Naarden, The Netherlands. Neuromuscul Disord 2003;13:757-64.), the target age was assumed to be adults, and in the Japanese version, the target age is stated because it includes children's ages as well.

Note 2: Section 6 - Renal function has been added in the Japanese version

KN-01
Medication Diary

Please bring this sheet at the next visit.

Next Visit：

Month:　　, Day:　　, Year: 201　

【Precaution of medication】

- Please take medicine (KN-01) three times a day after meals.
- If you forgot to take KN-01, please take it when you remember. Please take the next dose at the usual time (after meals). Please do not take KN-01 twice at once.
- We are planning to ask you the exact time you took the last meal on your next visit.

Your Name:_____

【Contact Information】

Medical Institution:

_____

Principal Investigator:

_____

Attending Doctor:

_____

CRC:

_____

Contact Information:

TEL: _____

In the case of nighttime / holiday,
you should call the emergency
outpatient with the same phone number.

【Example】

Medication Day	Morni		ng
2013 y. 10 m. 03 d.	■ (8 :00)	■ (12:00)	■ (19:00)
2013 y.		■ (12:00)	■ (19:00)
2013 y.		■ (12:00)	■ (19:00)
2013 y. 10 m. 04 d.	■ (8 :00)		
2013 y. 10 m. 05 d.	■ (8 :00)		
2013 y. 10 m. 06 d.	■ (8 :00)		
2013 y. 10 m. 07 d.	■ (8 :00)	■ (12:00)	■ (19:00)
2013 y. 10 m. 08 d.	■ (8 :00)	■ (12:00)	■ (19:00)
2013 y. 10 m. 09 d.	■ (8 :00)	■ (12:00)	■ (19:00)
2013 y. 10 m. 10 d.	■ (8 :00)	■ (12:00)	□ (:)
2013 y. 10 m. 11 d.	□ (:)	□ (:)	(:)
2013 y. 10 m. 12 d.	□ (		)
2013 y. 10 m. 13 d.	□ (		)
2013 y. 10 m. 14 d.	□ (		)

Please fill out the medication time.

Please fill out the medication day.

If you forget to take medication, it will be unchecked.

If the next visit date is October 10, 2013, 14 o'clock, please have a statement before noon on the day and come to the hospital.

If you take medicine from today until the next visit, please check.

Medication method： 3 times a day,

□ capsules once (□ gram) after meals

Medication Day	Morning	Noon	Evening
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)
201__y. __m. __d.	☐ (:)	☐ (:)	☐ (:)

If you take medicine from today until the next visit, please check.

Medication method : 3 times a day,

□ capsules once (□ gram) after meals

Medication Day	Morning	Noon	Evening
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)
201__y. __m. __d.	□ (　:　)	□ (　:　)	□ (　:　)

If you take medicine from today until the next visit, please check.

Medication method : 3 times a day,

□ capsules once (□ gram) after meals

Medication Day	Morning	Noon	Evening
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)
201__y. __m. __d.	□ (:)	□ (:)	□ (:)

If you take medicine from today until the next visit, please check.

Medication method : 3 times a day,

□ capsules once (□ gram) after meals

Summaries of Changes to the Protocol

■ Protocol

<table>
<tr><th>Revised Section</th><th>Before Revision (Ver.1.0, Created 7/24/2013)</th><th>After Revision (Ver.2.0, Created 12/5/2013)</th><th>Reason for</th></tr>
<tr><td>6.3.3 Allowed Concomitant Drugs and Treatments
[Rationale]</td><td>For drugs used in emergencies, especially in the status epilepticus, lifesaving treatment must be the priority, and limiting their use is difficult.</td><td>For drugs used in emergencies, lifesaving treatment must be the priority, and limiting their use is difficult.</td><td>Because lifesaving treatment must always be given priority and not just when the there is a high degree of convulsions (status epilepticus).</td></tr>
<tr><td>7.1 Observation and Examination Schedule Concomitant Drugs and Treatments Investigation</td><td>
<table>
<tr><td></td><td>Consent</td><td colspan="2">Period Before</td><td colspan="2">Observation Period</td></tr>
<tr><td></td><td></td><td colspan="2">- 1 week</td><td colspan="2">0 weeks</td></tr>
<tr><td>Day</td><td></td><td colspan="2">-7~0</td><td colspan="2">0</td></tr>
<tr><td>Co-Administered[10]</td><td>●</td><td>●</td><td>●</td><td>●</td><td>●</td></tr>
</table>
</td><td>
<table>
<tr><td></td><td>Consent</td><td>Period Before</td><td>Observation Period</td></tr>
<tr><td></td><td></td><td>- 1 week</td><td>0 weeks</td></tr>
<tr><td>Day</td><td></td><td>-7~0</td><td>0</td></tr>
<tr><td>Co-Administered[10]
Drug/Treatment Survey[10)]</td><td>●</td><td>●</td><td>●</td></tr>
</table>
</td><td>Adjusted format.</td></tr>
<tr><td>7.1.1 Observation of Stroke-like Episode and Severity
(2) MELAS Degree of Severity</td><td>Note that, at the time of evaluation of subjects for MELAS degree of severity, 12-lead electrocardiography and echocardiography (ejection fraction [EF], left ventricular diastolic dimension [LVDD], left ventricular systolic dimension [LVSD], LVSD, pulse wave Doppler [PWD], tricuspid regurgitation peak gradient [TRPG], asynergy, and valve) will be conducted.</td><td>Note that, at the time of evaluation of subjects for MELAS degree of severity, 12-lead electrocardiography and echocardiography (ejection fraction [EF], left ventricular diastolic dimension [LVDD], left ventricular systolic dimension [LVSD], pulse wave Doppler [PWD], tricuspid regurgitation peak gradient [TRPG], asynergy, and valve) will be conducted.</td><td>Deleted repetition in test item.</td></tr>
<tr><td>7.3.2 Secondary Endpoints for Efficacy
[Rationale]</td><td>(4) In a previous study,[3] blood/CSF taurine, lactate, and pyruvic acid levels, and lactate/pyruvic acid ratio decreased after taurine treatment.</td><td>(4) In a previous study,[3] blood/CSF taurine, lactate, and pyruvic acid levels, and lactate/pyruvic acid ratio increased after taurine treatment.</td><td>Corrected error.</td></tr>
<tr><td>7.4.2 Handling Vital Signs and Laboratory Tests</td><td></td><td>Note that these will not be treated as laboratory abnormalities as defined in Section 9.2.1 “Definition of Adverse Events.”</td><td>Addition per the 9.2.1 item revision.</td></tr>
</table>

9.2.1 Definition of Adverse Events		[Abnormal Lab Values] Biochemical examination: glucose and HbA_1c levels Blood tests: blood lactate (deproteinized) and blood pyruvic acid (deproteinized) levels CSF Tests: CSF lactate (deproteinized) and CSF pyruvic acid (deproteinized) levels Blood leukocyte tests: mitochondrial gene mutation rate, $tRNA^{Leu(UUR)}$ taurine modification rate, and NADH dehydrogenase 6 protein mass	Because the laboratory test abnormalities associated with MELAS are not handled as adverse events.
19. Costs Related to Trial Participation	Medical treatment related expenses, excluding the drugs that have the same efficacy and effect as the expected efficacy and effect of the investigational medicinal product during the clinical trial, shall be covered by health insurance treatment.	Expenses related to drugs other than the study drug during the clinical trial period or medical care other than the specified examination items will be fall under medical insurance.	Adjusted description.

■ Attachment 1

Revised Section	Before Revision (Created 7/9/2013)	After Revision (Created 10/2/2014)	Reason for Revision
24.3 Site Institutions and Clinical Trial Implementing Parties (Investigators)	Jichi Medical University Hospital, Internal Medicine of Neurology, Lecturer, Haruo Shimazaki (Lecturer) 3311-1 Yakushiji, Shimotsuke-shi, Tochigi-ken, 329-0498, Japan Phone: 0285-44-2111 Not noted Kurume University, Medical School Hospital, Prof. Yasutoshi Koga	Deleted Hiroshima University Hospital, Department of Neurology, Associate Professor of Medical Treatment, Tetsuya Takahashi 1-2-3 Kasumi, Minami-ku, Hiroshima-shi, Hiroshima-ken, 734-8551, Japan Phone: 082-257-5555 Kurume University, Medical School Hospital, Department of Pediatrics, Prof. Yasutoshi Koga	Revised, deleting and adding site institutions.
24.5.1 Contract Research Organization (2) Monitoring	DOT WORLD CO.,LTD. PMO Hatchobori Building 3-22-13 Hatchobori , Chuo-ku, Tokyo, 104-0032, Japan Phone: 03-3523-0210 Fax: 03-3523-0225 Responsible Party: Tetsuya Orito Clinical Research Associates: Namiko Murao, Keiko Onodera, Naoko Kataoka, Ayumi Kuramoto, Miho Araki [Main Tasks] Follow procedures according to separately created documents and conduct monitoring.	DOT WORLD CO.,LTD. PMO Hatchobori Building 3-22-13 Hatchobori , Chuo-ku, Tokyo, 104-0032, Japan Phone: 03-3523-0210 Fax: 03-3523-0225 Responsible Party: Tetsuya Orito Clinical Research Associates: Namiko Murao, Keiko Onodera, Naoko Kataoka, Ayumi Kuramoto, Miho Araki, Hiroko Iijima, Yukihisa Fujisawa, Mariko Shimobayashi, Yuki Yabe [Main Tasks] Follow procedures according to separately created documents and conduct monitoring.	Revised adding monitors.

■ Attachment 3

Revised Section	Before Revision (Created 6/19/2013)	After Revision (Created 12/5/2013)	Reason for Revision

◆Section 6: Renal function Note 2	0-Normal 1-Creatine clearance <50-90 ml/min/1.73 m^2 2- Creatine clearance 30-50 ml/min/1.73 m^2 3- Creatine clearance 10-30 ml/min/1.73 m^2 4- Creatine clearance <10 ml/min/1.73 m^2 or dialysis in needed	0-Normal 1-Creatinine clearance <50-90 ml/min/1.73 m^2 2-Creatinine clearance 30-50 ml/min/1.73 m^2 3-Creatinine clearance 10-30 ml/min/1.73 m^2 4-Creatinine clearance <10 ml/min/1.73 m^2 or dialysis in needed	Corrected error.

Underlined text: Revision Created 12/5/2013

KN01 Multicenter Multicenter Trial Focusing on

Mitochondrial Encephalomyopathy (MELAS)

Statistical Analysis Plan

Date of Creation: 10/7/2014

Clinical Trial Protocol Number: KN01-MELAS-01

Version Number: Version 1.0

Revision History

Version	Effective Date	Prepared/Revised by	Change Log
1.0	2014/10/7	Kazuhiro Saito	Created new document.

Approval Section

Position	Organization and Name	Signature
Coordinating Investigator	Kawasaki Medical School Division of Neurology Yoshihide Sunada	Stored separately.
Senior Statistician Responsible	DOT World Co., Ltd. Tatsuhiro Uenishi	Stored separately.
Associate Statistician	Takumi Information Technology Inc. Kazuhiro Saito	Stored separately.

Table of Contents

1. Trial Overview

1.1. Overview

In this clinical trial, the taurine treatment is performed to control any reoccurrence of a stroke-like episode for patients who suffer from the intractable disease mitochondrial encephalomyopathy (MELAS), in order to verify its efficacy and safety.

1.2. Study Design and Setting Rationale

This trial is a multicenter open-label study (Phase 3).

[Rationale for trial design]

A highly reliable, randomized, double-blind, placebo-controlled trial is not ethically possible in patients with MELAS as the average life expectancy after diagnosis is only 7.3 ± 5.0 years (Yatsuga S, Povalko N, Nishioka J, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Act 2012;1820:619-24).

1.3. Observation and Examination Schedule

The observations and examinations are conducted according to the following schedule.

		Consent	Pre-observation period		Observation period						When discontinued
			Week -1		Week 0		Week 4	Week 12	Week 24	Week 36	Week 52	
Day			-7 to 0		0		28	84	168	252	364	
Tolerance range (Days)							±7	±7	±14	±14	±14	
Acquired consent		●										
Patient background examination[1)]			●									
MRI of head			●[2)]					●[3)]			●	●
Enrollment				●								
Observation of number of stroke-like episodes								●[4)]				●[4)]
MELAS severity[5)] (12-lead ECG and cardiac echo)					●						●	●
Physical examination[6)]					●		●	●	●	●	●	●
In-hospital blood test[7)]	Hematological test				●		●	●	●	●	●	●
	Biochemical test				●		●	●	●	●	●	●
Special examination[8)]	Blood test				◎		◎				◎	◎
	CSF test[9)]				◎						◎	◎
	WBC test[9)]				◎						◎	◎
MMSE score					●						●	●
Investigational medicinal product prescription						●	●	●	●	●		
Checking status of taking investigational medicinal product						●	●	●	●	●	●	●
Checking for adverse events						●	●	●	●	●	●	●
Survey on Concomitant drugs and treatments[10)]		●	●	●	●	●	●	●	●	●	●	●

● Items performed/measured in-hospital, ◎: Concentrated measurement items

1) The following items are surveyed.

① Gender, date of birth and age of patient

② Number of stroke-like episodes over the past 78 weeks (Cases with co-administration of arginine occurred during co-administration period of arginine)

③ Mitochondria DNA point mutations (A3243G, T3271C, G3244A, T3258C and T3291C)

④ Blood pressure, pulse, height and weight

⑤ Complications and smoking history

⑥ Past medical history during previous 78 weeks prior to acquiring consent

2) Possible when taken within 4 weeks before start of administration of investigational medicinal product

3) Brain MRI is taken when a stroke-like episode occurs.

4) Check whether stroke-like episode occurs. The "MELAS stroke diagnostic criteria" is used to assess the stroke-like episode.

① and ② below must be fulfilled.

① In (1) through (6) below, when any of the abrupt-onset focal neurological deficits applies.

(1) Hemiplegia or monoplegia

(2) Cortical sensory disorder (Sensory extinction)

(3) Cortical visual disorder (Scintillating scotoma, cortical blindness)

(4) Aphasia

(5) Apraxia

(6) Agnosis

② High signal intensity is confirmed in a brain MRI diffusion weighted image.

5) MELAS severity is assessed in accordance with "Japanese Mitochondrial Disease Rating Scale (JMDRS)."

6) Measure the weight, temperature, as well as the blood pressure and pulse while in a quiet seated position.

7) Hematological test: RBC count, WBC count, blood platelet count, hemoglobin content, hematocrit level, hemogram

Biochemical test: total protein, albumin, glucose, HbA1c level, AST (GOT), ALT (GPT), ALP, LDH, γ-GTP, CK, T-Bil, D-Bil, BUN, Cre, uric acid, TG, T-Cho, Na, K, Cl

8) Blood test: Lactic acid in blood (Deproteinized), pyruvic acid in blood (Deproteinized), amino acid analysis in blood (39 types); measure using SRL.

CSF test: Lactic acid in CSF (Deproteinized), pyruvic acid in CSF (Deproteinized), amino acid analysis in CSF (39 types); measure using SRL.

WBC test: mitochondrial DNA mutation rate, $tRNA^{Leu(UUR)}$taurine modification rate, ND6 protein level; Measure at Kawasaki Medical School and Nippon Medical School – Institute of Gerontology

9) Optional (Voluntary measurement item)

10) The drugs used as well as the regimen, the co-administration period and the reason for co-administration is examined from 4 weeks prior to acquiring consent until the end of the observation period or until the discontinuation of the administration.

1.4. Expected Sample Size

The expected sample size is 15 cases.

1.4.1 Rationale for Setting Sample Size

The expected sample size was set based on the possibility of performing the following and the statistical study.

- The preparations involved in this trial were based on a survey of neurology and pediatrics departments throughout the country and the number of patients that could potentially be registered in this trial (patients who had at least 2 stroke-like episodes in the past year), which included 21 subjects of patients who were receiving the co-administration of arginine and 5 subjects of patients who were not receiving the co-administration of arginine. In addition to this, other inclusion and exclusion criteria are used to select trial participation and those patients who provided consent are registered. The actual number of subjects recruited was set for those who could participate based on the scheduled trial period.
- Two MELAS patients were administered taurine, and their recurring stroke-like episodes were completely controlled for over 9 years (Rikimaru et al. 2012). While there were few patients, the results showed a 100% responder rate, and therefore setting a 50% rate was assumed to be a conservative estimate.

- In patients currently being treated with off-label L-arginine, the number of stroke-like episodes almost never reaches zero. Therefore, as achievement of no stroke-like episodes after the study drug administration is an objective indicator showing treatment efficacy, the 100% responder rate was adopted as the primary endpoint.
- The patients in this trial have had at least two stroke-like episodes in the 78-week period prior to acquiring consent, and there were almost no cases where the number of stroke-like episodes was zero under the existing treatment regimen using off-label arginine. Accordingly, the threshold of 100% responder rate was assumed to be 5%.
  - When gathering 15 cases, a power of more than 90% can be secured (significance level of 5% on both sides) assuming 5% for a threshold responder rate of 100% and 50% for an expected responder rate of 100%. In addition, a power of more than 80% can be secured even for the 10 subjects with the co-administration of arginine and the 5 subjects without the co-administration of arginine.
- Efficacy in this clinical trial will be evaluated with the total cases. Further evaluation will be performed with no L-arginine Co-Administration and L-arginine Co-Administration subjects separately.

2. Analysis Objectives

2.1. Efficacy Analysis

The following endpoints are examined for FAS and PPS.

- Primary endpoints for efficacy (100% responder rate)
- Secondary endpoints for efficacy
- MMSE (Mini-Mental State Examination) score

2.2. Safety Analysis

The following endpoints are examined for the safety analysis set.

- Adverse events
- In-hospital blood test
- Physical examination

3. Data Sets for Analysis

3.1. Handling of Cases and Case Data

As a general rule, the following policy applies.

3.2. Analysis Set

As a general rule, the following policy applies. However, clinical conferences shall be held and the parties implementing the clinical trial shall decide the policy when necessary based on the opinions and feedback from medical specialists.

3.2.1. Cases with Acquired Consent

All the subjects whose consent was acquired for participation in this trial shall be cases with acquired consent.

3.2.2. Registered Subjects

Subjects who are recognized as eligible after acquiring consent.

3.2.3. FAS

Full analysis set from all enrolled subjects excluding subjects for which the following applies.

- Subjects with maximum GCP deviation
- Subjects who received no administrations of the investigational medicinal product
- Subjects without any efficacy related assessment

3.2.4. PPS

Analysis set from FAS excluding subjects for which the following applies.

PPS analysis is performed in order to check the robustness of the results from the FAS analysis.

- Subjects for whom the inclusion criteria do not apply and who meet the exclusion criteria
- Subjects whose administration of the investigational medicinal product does not meet 26 weeks
- Subjects with a drug compliance for the investigational medicinal product that is less than 70%

3.2.5. Safety Analysis Set

Among the registered subjects, this set refers to those who have been administered the investigational medicinal product more than once. However, when an adverse event appears or it is discovered that the case meets the exclusion criteria after being administered the investigational medicinal product, the case shall be included in the analysis set.

3.3. Handling of Missing Values, Outliers and Other

The missing values and outliers as well as the definitive handling during the period in the

analysis are determined until the data is fixed when necessary based on the opinions and feedback from medical specialists. The cases and values excluded from the analysis are included in the summary tables for individual values, but excluded from the calculation for the descriptive statistics, etc.

3.4. Handling of Date Data

When calculating each measurement, data that match the acceptable range shown below are used. Complementing with data outside of the acceptable range, will be examined to determine their acceptability in the clinical conferences. However, when multiple observed values correspond to the same analysis period, the period close to the reference day is used. When the number of days up to the reference day is the same, the observed values farthest from the date are used.

Refer to 1.3 for the acceptable range.

3.5. Handling of Discontinuation Data

The data up to the discontinuation of administration is used in the analysis. However, for adverse events, data to 28 days after the investigational medicinal product has stopped is used in the analysis.

4. Statistical and Analytical Issues

4.1. Adjusting for Covariance

Adjusting for covariance is not performed.

4.2. Interim Analysis

Interim analysis is not performed.

4.3. Multicenter Trial

In this trial, the plan is executed at a total of 13 facilities and collected data on a total of 15 cases. The calculation of the endpoints based on a single facility is not performed because there are few cases per facility. The subject ID numbers in the case summary table and the facility name summary table are created so that the facility for each case can be identified. (Refer to 9.1 for other diagrams and tables)

4.4. Significance Level

The significance level shall be 5% on both sides. In addition, the confidence level when calculating the confidence interval shall be 95%.

4.5. Multiple Comparisons and Multiplicity

Adjusting for multiplicity is not performed in this trial.

4.6. Total and Separate Examinations

In this clinical trial, total cases will be evaluated. Further evaluation will be performed with no L-arginine Co-Administration and L-arginine Co-Administration subjects separately.

4.7. Statistical Method

4.7.1. Summary Statistics

Unless indicated otherwise, the sample size, arithmetic mean, standard deviation, minimum value, median value and maximum value are calculated for continuous values, and the number of digits shown are established as follows.

Arithmetic mean, median value	The last 2 significant digits of the measurement value are rounded and the value is displayed up to the last digit.
Standard deviation	The last three significant digits of the measurement value are rounded and the value is displayed up to the last 2 digits.
Maximum value, minimum value	Significant digits of the measurement value.

4.7.2. Frequency Calculation

Unless indicated otherwise, the percentage (%) for the category values is obtained for the aggregation of frequency and the number of cases for analysis. The percentage (%) is rounded to the first decimal place and is displayed up to the one's place.

4.7.3. Confidence Interval for Percentage

Unless indicated otherwise, the confidence interval is assumed to have an accuracy of 95% based on the Clopper-Pearson method as a confidence interval for the percentage.

4.7.4. Logistic Regression Analysis

The following analysis is performed for logistic regression.

- The 100% responder or the 50% responder shall be response variables, and the cases that correspond to those responders are handled as events in the logistic regression model.
- There shall only be one factor specified in each analysis model.
- When the factor is a category value, the odds ratio shows how many times the value is multiplied for the other levels that are not the odds for a specified level. The 95% confidence interval and the p-value are calculated for that odds ratio. Firth correction is applied when necessary.

- When the factor is a continuous value, the odds ratio shows how many times the value is multiplied when the unit value, which is specified by the factor value, increases. The 95% confidence interval and the p-value are calculated for that odds ratio. Firth correction is applied when necessary.
- The odds ratio and its 95% confidence interval are rounded to the third decimal place and is displayed up to the third decimal place.
- The p-value is rounded to the fifth decimal place and is displayed up to the fourth decimal place. However, when the value is less than 0.0001 before being rounded, the “<0.0001” is displayed.

4.7.5. Aggregation Method

- Aggregating the regimen with and without the co-administration of arginine is performed for the total analysis set, for the regimen with and without co-administration of arginine (Total of 3 types).
- The aggregation is performed in the analysis sets that are established in Chapters 5, 6, 7 and 8. Unless there is no special notation, the aggregation is performed for both with or without the co-administration of arginine in the aggregation and analysis for these chapters.

4.7.6. Software Used

The following software is used.

OS	:	Windows 7
Statistical analysis	:	SAS (Ver. 9.3)

4.7.7. Glossary of Adverse Events

The event names are based on the preferred terms (PT) in the MedDRA code, and the organ names are based on the system organ class (SOC). In addition, Version 17.1 is used for MedDRA.

4.7.8. Drug Name Codes

The drug names use the codes from the data file for medicine names.

5. Trial Subjects

5.1. Breakdown of Subjects and Completion of Trial

5.1.1. Breakdown of Subjects

Analysis Range

Cases with Acquired Consent

Aggregation Table

・ The frequency is aggregated for the cases with acquired consent, the enrolled subjects and the subjects omitted before registration.

In addition, the frequency is aggregated for the FAS, PPS and the safety analysis set (T050101), and the percentage is obtained for the enrolled subjects.

Graph

・ The frequency is aggregated for the breakdown of the subjects shown below, and a flow chart is created (F050101).

Breakdown of Subjects	Definitions of Subjects
Cases with acquired consent	-
Enrolled subjects	-
Subjects omitted before registration	Subjects that were not enrolled of the cases whose consent was acquired
Subjects used in safety analysis set	-
Subjects not used in safety analysis set	Subjects that are not used in the safety analysis set from the registered subjects
Subjects used in FAS	-
Subjects not used in FAS	Subjects that are not used in the FAS from the enrolled subjects
Subjects used in PPS	-
Subjects not used in PPS	Subjects from the FAS that were not used in the PPS

Summary Table

・ A table that summarizes the inclusion and exclusion criteria for the subjects that were not enrolled of the cases whose consent were acquired is provided.

5.1.2. Discontinued Cases

Analysis Range

Registered Subjects

Calculation Table

・ The percentage is obtained for the number of completed cases, discontinued cases and cases for analysis. In addition, with regard to the discontinued cases, the percentage of the number of subjects per reason for discontinuation and ratio to the number of cases for analysis (T050102).

Summary Table

・ The administration start date, the discontinuation date and the reason for discontinuing are shown in a summary table for the discontinued cases.

5.2. Deviation from Protocol

Analysis Range

Cases with Acquired Consent

Summary Table

- A summary table shows the reason for deviation for the cases that deviated from the Protocol (L0502).

5.3. Subjects Excluded from Analysis Sets

Summary Table

- The enrolled subjects are analyzed and a summary table is created for subjects excluded from the safety analysis set (L0503).
- The enrolled subjects are analyzed and a summary table is created for subjects excluded from FAS (L0503).
- The FAS is analyzed and a summary table is created for subjects excluded from PPS (L0503).

5.4. Administration Status

Analysis Range

FAS

Aggregation method

Aggregation Table

・ The summary statistics (T0504) is obtained for the number of days of administration and the drug compliance (%).

Summary Table

・ A summary is created for the administration status (L0504) per case.

6. Patient Background

Analysis Range

FAS, PPS and Safety Analysis Set

Analysis Items

・ Gender (Male, Female)

・ Age (years old)

・ Age (10-<20years old, 20-<30 years old, 30-<40 years old, 40-<50 years old)

- Appearance of stroke-like episodes in the 78 weeks* before acquiring consent (Frequency of appearance is made a category)
- Usage status of arginine intravenous drug (Not used, used)
- Mitochondria DNA point mutation: A3243G (None, present)
- Mitochondria DNA point mutation: T3271C (None, present)
- Mitochondria DNA point mutation: G3244A (None, present)
- Mitochondria DNA point mutation: T3258C (None, present)
- Mitochondria DNA point mutation: T3291C (None, present)
- Systolic pressure (mmHg)
- Diastolic pressure (mmHg)
- Pulse (BPM)
- Height (cm)
- Weight (kg)
- Weight (<15 kg, 15-<25 kg, 25-<40 kg, 40 kg -)
- Complications (None, present)
- Smoking history (No smoking history, currently smoking and smoked previously)
- Past medical history in the 78 weeks* before acquiring consent (None, present)

*Usage period for arginine oral drug (after week 26 and before week 78) for subjects who continue to use arginine oral drug

Aggregation Table

・ Summary statistics are obtained for the continuous values of the analysis items. The frequency is aggregated for the category value (T06).

Summary Table

・ A summary of the subject’s history is created (T06_01).

・ A summary on the occurrence of stroke-like episodes in the 78 weeks before acquiring consent (Frequency of occurrence is made a category) (T06_02).

・ A summary is created for the mitochondria (T06_05) DNA point mutations.

・ A summary of the height and weight is created.

7. Efficacy Analysis

Analysis Range

FAS

Summary Table

・ The FAS is analyzed and a summary is created for the efficacy (L0701).

・ The FAS is analyzed and a summary is created for the episodes and the occurrence of other symptoms after administration (L0704).

・ The FAS is analyzed and a summary is created for the episodes and the appearance of other symptoms before administration (L0704).

7.1. Primary Endpoints for Efficacy (100% Responder Rate)

Analysis Range

FAS and PPS

Aggregation Method

・ The cases without any stroke-like episodes (0 times) during the evaluation period (from week 9 after starting the administration of the investigational product until its administration is completed) shall have a 100% responder rate.

Aggregation Table

・ The frequency of the 100% responder is aggregated and the confidence interval (T0701_01) for the percentage is obtained.

・ Logistic regression analysis is performed with the 100% responder as the response variable.

The specified factors as well as the comparison method and units are as follows (T0701_02).

Factor	Comparison / Unit
Gender	Female or male
Age when consent is acquired – years old	+10 years old
Frequency of stroke-like episodes in the 78 weeks* before acquiring consent	+1 time
Complications	None or present
Smoking history	No smoking history or currently smoking
	No smoking history or smoked previously
Past medical history in the 78 weeks* before acquiring consent	None or present
Taurine blood concentration (Week 0)	+100 nmol/mL
Taurine blood concentration (Week 52)	+100 nmol/mL
Arginine blood concentration (Week 0)	+100 nmol/mL

Factor	Comparison / Unit
Arginine blood concentration (Week 52)	+100 nmol/mL
Mitochondrial DNA mutation rate (Week 0)	+10%
Mitochondrial DNA mutation rate (Week 52)	+10%
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 0)	+0.1 folds
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 52)	+0.1 folds
ND6 protein level (Week 0)	+10 pg/mL
ND6 protein level (Week 52)	+10 pg/mL
Lactic acid in blood (Week 0)	+10 mg/dL
Lactic acid in blood (Week 52)	+10 mg/dL
Lactic acid in CSF (Week 0)	+10 mg/dL
Lactic acid in CSF (Week 52)	+10 mg/dL
Pyruvic acid in blood (Week 0)	+0.1 mg/dL
Pyruvic acid in blood (Week 52)	+0.1mg/dL
Pyruvic acid in CSF (Week 0)	+0.1 mg/dL
Pyruvic acid in CSF (Week 52)	+0.1 mg/dL
Ratio of lactic acid and pyruvic acid in blood (Week 0)	+1

Factor	Comparison / Unit
Ratio of lactic acid and pyruvic acid in blood (Week 52)	+1
Ratio of lactic acid and pyruvic acid in CSF (Week 0)	+1
Ratio of lactic acid and pyruvic acid in CSF (Week 52)	+1
JMDRS (Week 0)	+10
JMDRS (Week 52)	+10

・ The following subjects are analyzed, and the frequency of the 100% responder is calculated and the confidence interval for the percentage is obtained (T0701_03).

Analysis Subjects
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 78 week period before acquiring consent
Subjects who have at least two local neurological signs (regardless of confirmation of high signal intensity in MRI image of head) in the 78 week period before acquiring consent and subjects who have at least one local neurological sign (confirmed high signal intensity in MRI image of head)
Subjects who have at least two local neurological signs (regardless of confirmation of high

Analysis Subjects
signal intensity in MRI image of head) in the 78 week period before acquiring consent
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 52 week period before acquiring consent
Subjects who have at least two local neurological signs (regardless of confirmation of high signal intensity in MRI image of head) in a 52 week period before acquiring consent

7.2. Secondary Endpoints for Efficacy (1) Improvement or Presence of Clinical Symptoms

Analysis Range

FAS and PPS

Aggregation Method

・ In this analysis, a score is aggregated for the regimens with and without the co-administration of arginine during each period, totally and separately (2 types for week 0 and week 52).

Aggregation Table

・ The frequency is aggregated for the score in each section. However, the frequency is aggregated for the score per section when the section details are present. In addition, the

summary statistics are calculated for the total score per section and total score overall. The sections, section details and the scores (T0702_01) are as follows.

Section	Section Details	Score
Section1	Speech	0, 1, 2, 3, 4
	Swallowing	0, 1, 2, 3, 4
	Handwriting	0, 1, 2, 3, 4
	Cutting food – Handling utensils (Hand motor skills)	0, 1, 2, 3, 4
	Dressing	0, 1, 2, 3, 4
	Hygiene	0, 1, 2, 3, 4
	Falling	0, 1, 2, 3, 4
	Paroxysmal event (migraine, seizures)	0, 1, 2, 3, 4
Section2	Proximal muscle strength (modified MRC)	0, 1, 2, 3, 4, 5
	Upper limbs coordination	0, 1, 2, 3, 4
	Walking	0, 1, 2, 3, 4

Section	Section Details	Score
	Moderate motor activities (such as vacuum cleaning, carrying groceries, climbing one flight of stairs, preparing your own bed)	0, 1, 2, 3, 4
	Vigorous motor activities (such as running, climbing several flights of stairs or participation on other strenuous sports)	0, 1, 2, 3, 4
Section3:	Vision	0, 1, 2, 3, 4, 5
	Hearing	0, 1, 2, 3, 4
Section4	Endocrine disorder	0, 1, 2, 3
Section5	Cardiac complication	0, 1, 2, 3, 4
Section6	Renal function	0, 1, 2, 3, 4
Section7	Mental retardation	0, 1, 2, 3, 4
	Motivation and drive	0, 1, 2, 3, 4

Summary Table

・ FAS is analyzed and a summary is created for the Section Table 1 for the improvement or persistence of clinical symptoms (Japanese Mitochondrial Disease Rating Scale (JMDRS).

・ FAS is analyzed and a summary is created for the Section Tables 2 and 3 for the improvement or persistence of clinical symptoms (JMDRS) (L0702_01).

・ FAS is analyzed and a summary is created for the Section Tables 4 to 7 for the improvement or persistence of clinical symptoms (JMDRS) (L0702_01).

7.3. Secondary Endpoints for Efficacy (2) 50% Responder Rate

Analysis Range

FAS and PPS

Calculation Method

・ The 50% responders are cases showing a decrease of more than 50% in the number of stroke-like episodes over 4 weeks during the evaluation period after administering the investigational product when compared to before its administration.

Calculation Table

・ The frequency of the 50% responder is aggregated and the confidence interval for the percentage is obtained (T0702_02).

・ Logistic regression analysis is performed with the 50% responder as the response variable. The specified factor, comparison method and unit (T0701_02) shall be the same as the primary endpoints (100% responder).

7.4. Secondary Endpoints for Efficacy (3) Frequency of Abrupt-onset Focal Neurological Deficits (Regardless of Confirmation of High Signal Intensity in MRI Diffusion Weighted Image of Head) During Episode Based on MELAS Stroke Assessment Criteria

Analysis Object

FAS and PPS

Aggregation Method

- In this analysis, the appearance of signs is calculated for the regimens with and without the co-administration of arginine before and after administration, totally and separately (2 types for before and after administration).
- The incidence rate is the number of episodes that is averaged out per month during the extended observation period (month). Note that one month is equal to 28 days. In addition, the number of extended observation days is aggregated as follows: Final observation day for week 52 (or when administration was discontinued) – Administration start day + 1.

Calculation Table

- The frequency is aggregated as a category for the number of appearances collected in the data. In addition, the summary statistics(T0702_03) are obtained for the incidence rate, and the

number of digits is established for showing the valid digits of the incidence rate, which is rounded to the second decimal place (including the second decimal place).

7.5. Secondary Endpoints for Efficacy (4) Special Examination

Analysis Range

FAS and PPS

Calculation Method

・ In this analysis, data is aggregated in a special examination for the regimens with and without the co-administration of arginine during each period, totally and separately (2 types for week 0 and week 52 (or when administration was discontinued)). The rate of change (%) in this analysis is the corresponding analysis set, which applies to the subjects without missing values in week 0 and week 52 (or when administration was discontinued), and it is calculated using the following formula.

$$100 \times \frac{\text{Value for week 52 (or when administration was discontinued)} - \text{Value for week 0}}{\text{Value for week 0}}$$

Aggregation Table

・ The summary statistics are calculated for the special examinations noted below. In addition, the summary statistics are obtained for the rate of change between the regimens with and

without the co-administration of arginine. The number of significant digits for the rate of change (%) is rounded to the tenths place (including the tenths place) (T0702_04).

Special Examination
Lactic acid level in blood
Lactic acid level in CSF
Pyruvic acid level in blood
Pyruvic acid level in CSF
Ratio of lactic acid and pyruvic acid in blood
Ratio of lactic acid and pyruvic acid in CSF
Taurine level in blood
Taurine level in CSF

Graph

- A trend diagram is created for the FAS with the taurine in the blood and the arginine concentration on the vertical axis and the number of days on the horizontal axis (G0702_04).
- A trend diagram is created for the FAS with the taurine in the CSF and the arginine concentration on the vertical axis and the number of days on the horizontal axis (G0702_04).

・ A trend diagram is created for the FAS with the special examination values noted below on the vertical axis and the number of days on the horizontal axis (G0702_05).

Special Examination
Lactic acid level in blood
Pyruvic acid level in blood
Ratio of lactic acid and pyruvic acid in blood
Lactic acid value in CSF
Pyruvic acid value in CSF
Ratio of lactic acid and pyruvic acid in CSF
Mitochondrial DNA mutation rate
$tRNA^{Leu(UUR)}$ taurine modification rate
ND6 protein level

Summary Table

・ The FAS is analyzed and a summary is created for the special examinations (L0702_04).

7.6. Secondary Endpoints for Efficacy (5) Imaging Scan (MRI Scan of Head)

Analysis Range

FAS and PPS

Aggregation Method

- This analysis includes the corresponding analysis set, which applies to the subjects without missing imaging test results in week 0 and week 52 (or when administration was discontinued).
- In the shift table, the frequency is aggregated combining the imaging test results (also including the total) for week 0 and week 52 (or when administration was discontinued).

Aggregation Table

- A shift table is created for the imaging scan results (T0702_05_a) from the diffusion-weighted image (axial) noted below.
- A shift table is created for the other imaging scan results besides the diffusion-weighted image (axial) noted below (T0702_05_b).

Imaging Scan	Imaging Scan Results
Diffusion weighted image (axial)	Normal, abnormal (confirmed high signal intensity), abnormal (other), not taken

Imaging Scan	Imaging Scan Results
MRA image (intracranial)	Normal, abnormal, not taken
FLAIR image (axial)	Normal, abnormal, not taken
T2 weighted image (axial)	Normal, abnormal, not taken
T1 weighted image (axial)	Normal, abnormal, not taken
T2* weighted image (axial)	Normal, abnormal, not taken
ADC map	Normal, abnormal, not taken

Summary Table

・ The FAS is analyzed and a summary is created for the imaging scans (L0702_05_01、L0702_05_02).

7.7. Secondary Endpoints for Efficacy (6) Times Arginine Intravenous Drug Was Used Before and After the Administration of the Investigational Product

Analysis Range

FAS and PPS

Calculation Method

・ In this analysis, the frequency of administration is aggregated for the regimens with and without the co-administration of arginine before and after administration, totally and separately (2 types for before and after administration).

・The abovementioned aggregation is performed when the episode definition is not referenced using the MRI check and when the MRI check is referenced.

Aggregation Table

・ The frequency is aggregated as a category for the extended frequency of administration collected in the data.

In addition, the frequency of administration per one episode by finding the frequency aggregation and ratio to the total number of episodes (T0702_06).

Summary Table

・ The FAS is analyzed and a summary is created for the usage status of the arginine intravenous drug before and after the administration of the investigational product.

7.8. Secondary Endpoints for Efficacy (7) Number of Confirmed High Intensity Signals When MRI of Head is Conducted After Subject Suffers from Headaches, Nausea, Vomiting, Convulsions and Disorder of Consciousness

Analysis Range

FAS and PPS

Calculation Table

・ The frequency is calculated as a category for the number of high signal intensity checks collected in the data (T0702_07).

7.9. MMSE (Mini-Mental State Examination) Score

Analysis Range

FAS and PPS

Calculation Method

・ In this analysis, an MMSE score is calculated for the regimens with the total subjects. It is further calculated for the regimens with and without the co-administration of arginine during each period separately (2 types for week 0 and week 52 (or when administration was discontinued).

Calculation Table

· The frequency is calculated for the MMSE score noted below. In addition, the summary statistics are calculated for the MMSE score total. The MMSE scores and the corresponding categories are as follows (T0703).

MMSE Score	Score Category
Time orientation	0, 1, 2, 3, 4, 5
Location orientation	0, 1, 2, 3, 4, 5
Immediate recall	0, 1, 2, 3
Calculation	0, 1, 2, 3, 4, 5
Delayed recall	0, 1, 2, 3
Naming of objects	0, 1, 2
Sentence repetition	0, 1
Oral instructions	0, 1, 2, 3
Written instructions	0, 1
Spontaneous writing	0, 1
Figure imitation	0, 1

Summary Table

· The FAS is analyzed and a summary is created for the MMSE score.

8. Safety Analysis

8.1. Adverse Events

Analysis Range

Safety Analysis Set

Calculation Method

- Adverse events are calculated when they appear after the administration of the investigational product has started and up to a period of 28 days after it has stopped being administered.
- The adverse event names are codified using the MedDRA, the preferred terms (PT) based on the MedDRA code are used, and the organ names are used based on the system organ class (SOC).
- The events that appear after the investigational product administration has started are handled as adverse events. Among the adverse events, those events whose causal relationship with the investigational product cannot be denied (“1. Clearly relationship,” “2. Possible relationship” and “Relationship cannot be denied”) are handled as adverse reactions.
- In the calculation for severity classification, when multiple adverse events are observed in the same subject, the most severe adverse event is counted.

・ In the aggregation by SOC, by PT and by severity classification, when multiple adverse events (or adverse reactions) are observed for the same subject, same SOC and same PT, the most severe adverse event (or adverse reaction) will be counted.

・ In the aggregation for classifying the relationship with the investigational product, when multiple adverse events are observed in the same subject and their relationship with the investigational product is mixed with “Related” and “Unrelated”, the result is counted as “Related.”

Calculation Table

・ The frequency (T080101_01) for the number of appearances is calculated for the following items and the adverse events are summarized.

Item
All adverse events
Serious adverse event
Fatal case
Adverse event causing discontinuation
Severity (Mild, moderate and serious)
Relationship with investigational

Item
medicinal product (None, present)

・ The frequency is aggregated for all adverse events and for adverse events by SOC, by PT and by severity (T080101_02).

Summary Table

・ A summary of the adverse events is created (L080101).

・ A summary of the fatalities is created (L080101).

・ A summary of the serious adverse events is created (L080101).

・ A summary of the adverse events causing discontinuation is created.(L080101).

8.2. Clinical Examination

Analysis Object

Safety Analysis Set

Aggregation Method

・ In this analysis, the values in the clinical examination are aggregated for the regimens with and without the co-administration of arginine during each period (6 types for week 0, week 4, week 12, week 24, week 36 and week 52 (or when administration was discontinued)).

・ Calculation Table

- The summary statistics are calculated for the hematological tests (in-hospital) noted below (T080102).

Hematological Test (In-hospital)
RBC count
WBC count
Blood platelet count
Hemoglobin content
Hematocrit level
Neutrophils
Lymphocytes

- The summary statistics are calculated for the biochemical tests (in-hospital) noted below (T080102).

Biochemical Test (In-hospital)
Total protein
Albumin
Glucose
HbA1c value

Biochemical Test (In-hospital)
AST (GOT)
ALT (GPT)
ALP
LDH
γ-GTP
CK
T-Bil
D-Bil
BUN
Cre
eGFR
Uric acid
TG
T-Cho
Na
K

Biochemical Test (In-hospital)
Cl

Graph

・A trend diagram is created with the hematological test on the vertical axis and with the number of days on the horizontal axis (G080101).

・A trend diagram is created with the biochemical test on the vertical axis and with the number of days on the horizontal axis (G080101).

Summary Table

・A summary of hematological test (in-hospital) is prepared (L080102_01).

・A summary of biochemical tests (in-hospital) is prepared (L080102_01).

・A summary of blood amino acid analyses (39 types) for blood test (SRL measurement) is prepared (L080102_02).

・A summary of CSF amino acid analyses (39 types) for CSF test [Given test] (SRL measurement) is prepared (L080102_02).

・ A summary (Measurements from Kawasaki Medical School, Nippon Medical School – Institute of Gerontology) for the WBC [Voluntary test] is prepared.

8.3. Physical Examination

Analysis Object

Safety Analysis Set

Calculation Method

- In this analysis, the values in the physical examination are calculated during each period (6 types for week 0, week 4, week 12, week 24, week 36 and week 52 (or when administration was discontinued)).
- Aggregation Table
- The summary statistics are obtained for the physical examination noted below (T080103).

Physical Examination
Systolic pressure
Diastolic pressure
Pulse
Weight
Body temperature

Graph

- A trend diagram is created with the physical examination on the vertical axis and with the number of days on the horizontal axis (G080103).

Summary Table

- A summary of the physical examination is created.

9. Appendix

9.1. Other Diagrams and Charts

Summary Table

- The safety analysis set(L0901_01) is analyzed, and a summary of the past medical history is created.
- The safety analysis set is analyzed, and a summary of the complications is created (L0901_02).
- The safety analysis set is analyzed, and a summary of the concomitant drugs is created (L0901_02) (L0901_03).
- The safety analysis set is analyzed, and a summary of the concomitant treatments is created (L0901_02) (L0901_04).

- The cases with acquired consent (L0901_05) are analyzed, and a summary is created for cases that are accepted or rejected.

KN01 Multicenter Multicenter Trial Focusing on

Mitochondrial Encephalomyopathy (MELAS)

Statistical Analysis Plan

Date of Creation: 2/2/2015

Clinical Trial Protocol Number: KN01-MELAS-01

Version Number: Version 1.1

Revision History

Version	Effective Date	Prepared/Revised by	Change Log
1.0	2014/10/7	Kazuhiro Saito	Created new document.
1.1	2015/2/2	Kazuhiro Saito	Unified notation and clarified definitions and clarified definitions.

Approval Section

Position	Organization and Name	Signature
Coordinating Investigator	Kawasaki Medical School Division of Neurology Yoshihide Sunada	Stored separately.
Senior Statistician Responsible	DOT World Co., Ltd. Tatsuhiro Uenishi	Stored separately.
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Table of Contents

1. Trial Overview

1.1. Overview

In this clinical trial, the taurine treatment is performed to control any reoccurrence of a stroke-like episode for patients who suffer from the intractable disease mitochondrial encephalomyopathy (MELAS), in order to verify its efficacy and safety.

1.2. Study Design and Setting Rationale

This trial is a multicenter open-label study (Phase 3).

[Rationale for trial design]

A highly reliable, randomized, double-blind, placebo-controlled trial is not ethically possible in patients with MELAS as the average life expectancy after diagnosis is only 7.3 ± 5.0 years (Yatsuga S, Povalko N, Nishioka J, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. Biochim Biophys Act 2012;1820:619-24).

1.3. Observation and Examination Schedule

The observations and examinations are conducted according to the following schedule.

		Consent	Pre-observation period		Observation period						When discontinued
			Week -1		Week 0		Week 4	Week 12	Week 24	Week 36	Week 52	
Day			-7 to 0		0		28	84	168	252	364	
Tolerance range (Days)							±7	±7	±14	±14	±14	
Acquired consent		●										
Patient background examination[1)]			●									
MRI of head			●[2)]			●[3)]					●	●
Enrollment				●								
Observation of number of stroke-like episodes						●[4)]						●[4)]
MELAS severity[5)] (12-lead ECG and cardiac echo)					●						●	●
Physical examination[6)]					●		●	●	●	●	●	●
In-hospital blood test[7)]	Hematological test				●		●	●	●	●	●	●
	Biochemical test				●		●	●	●	●	●	●
Special examination[8)]	Blood test				◎		◎				◎	◎
	CSF test[9)]				◎						◎	◎
	WBC test[9)]				◎						◎	◎
MMSE score					●						●	●
Investigational medicinal product prescription						●	●	●	●	●		
Checking status of taking investigational medicinal product						●	●	●	●	●	●	●
Checking for adverse events						●	●	●	●	●	●	●
Survey on Concomitant drugs and treatments[10)]		●	●	●	●	●	●	●	●	●	●	●

● Items performed/measured in-hospital, ◎: Concentrated measurement items

1) The following items are surveyed.

① Gender, date of birth and age of patient

② Number of stroke-like episodes over the past 78 weeks (Cases with co-administration of arginine occurred during co-administration period of arginine)

③ Mitochondria DNA point mutations (A3243G, T3271C, G3244A, T3258C and T3291C)

④ Blood pressure, pulse, height and weight

⑤ Complications and smoking history

⑥ Past medical history during previous 78 weeks prior to acquiring consent

2) Possible when taken within 4 weeks before start of administration of investigational medicinal product

3) Brain MRI is taken when a stroke-like episode occurs.

4) Check whether stroke-like episode occurs. The "MELAS stroke diagnostic criteria" is used to assess the stroke-like episode.

① and ② below must be fulfilled.

① In (1) through (6) below, when any of the abrupt-onset focal neurological deficits applies.

(1) Hemiplegia or monoplegia

(2) Cortical sensory disorder (Sensory extinction)

(3) Cortical visual disorder (Scintillating scotoma, cortical blindness)

(4) Aphasia

(5) Apraxia

(6) Agnosis

② High signal intensity is confirmed in a brain MRI diffusion weighted image.

5) MELAS severity is assessed in accordance with "Japanese Mitochondrial Disease Rating Scale (JMDRS)."

6) Measure the weight, temperature, as well as the blood pressure and pulse while in a quiet seated position.

7) Hematological test: RBC count, WBC count, blood platelet count, hemoglobin content, hematocrit level, hemogram

Biochemical test: total protein, albumin, glucose, HbA1c level, AST (GOT), ALT (GPT), ALP, LDH, γ-GTP, CK, T-Bil, D-Bil,, BUN, Cre, uric acid, TG, T-Cho, Na, K, Cl

8) Blood test: Lactic acid in blood (Deproteinized), pyruvic acid in blood (Deproteinized), amino acid analysis in blood (39 types); measure using SRL.

CSF test: Lactic acid in CSF (Deproteinized), pyruvic acid in CSF (Deproteinized), amino acid analysis in CSF (39 types); measure using SRL.

WBC test: mitochondrial DNA mutation rate, $tRNA^{Leu(UUR)}$taurine modification rate, ND6 protein level; Measure at Kawasaki Medical School and Nippon Medical School – Institute of Gerontology

9) Optional (Voluntary measurement item)

10) The drugs used as well as the regimen, the co-administration period and the reason for co-administration is examined from 4 weeks prior to acquiring consent until the end of the observation period or until the discontinuation of the administration.

1.4 Expected Sample Size

The expected sample size is 15 cases.

1.4.1 Rationale for Setting Sample Size

The expected sample size was set based on the possibility of performing the following and the statistical study.

- The preparations involved in this trial were based on a survey of neurology and pediatrics departments throughout the country and the number of patients that could potentially be registered in this trial (patients who had at least 2 stroke-like episodes in the past year), which included 21 subjects of patients who were receiving the co-administration of arginine and 5 subjects of patients who were not receiving the co-administration of arginine. In addition to this, other inclusion and exclusion criteria are used to select trial participation and those patients who provided consent are registered. The actual number of subjects recruited was set for those who could participate based on the scheduled trial period.
- Two MELAS patients were administered taurine, and their recurring stroke-like episodes were completely controlled for over 9 years (Rikimaru et al. 2012). While there were few

patients, the results showed a 100% responder rate, and therefore setting a 50% rate was assumed to be a conservative estimate.

- In patients currently being treated with off-label L-arginine, the number of stroke-like episodes almost never reaches zero. Therefore, as achievement of no stroke-like episodes after the study drug administration is an objective indicator showing treatment efficacy, the 100% responder rate was adopted as the primary endpoint.
- The patients in this trial have had at least two stroke-like episodes in the 78-week period prior to acquiring consent, and there were almost no cases where the number of stroke-like episodes was zero under the existing treatment regimen using off-label arginine. Accordingly, the threshold of 100% responder rate was assumed to be 5%.
- When gathering 15 cases, a power of more than 90% can be secured (significance level of 5% on both sides) assuming 5% for a threshold responder rate of 100% and 50% for an expected responder rate of 100%. In addition, a power of more than 80% can be secured even for the 10 cases with the co-administration of arginine and 5 cases without the co-administration of arginine.
- Efficacy in this clinical trial will be evaluated with the total cases. Further evaluation will be performed with no L-arginine Co-Administration and L-arginine Co-Administration subjects separately.

2. Analysis Objectives

2.1. Efficacy Analysis

The following endpoints are examined for FAS and PPS.

- Primary endpoints for efficacy (100% responder rate)
- Secondary endpoints for efficacy
- MMSE (Mini-Mental State Examination) score

2.2. Safety Analysis

The following endpoints are examined for the safety analysis set.

- Adverse events
- In-hospital blood test
- Physical examination

3. Data Sets for Analysis

3.1. Handling of Cases and Case Data

As a general rule, the following policy applies.

3.2. Analysis Set

As a general rule, the following policy applies. However, clinical conferences shall be held and the parties implementing the clinical trial shall decide the policy when necessary based on the opinions and feedback from medical specialists.

3.2.1. Cases with Acquired Consent

All the subjects whose consent was acquired for participation in this trial shall be cases with acquired consent.

3.2.2. Registered Subjects

Subjects who are recognized as eligible after acquiring consent.

3.2.3. FAS

Full analysis set from all enrolled subjects excluding subjects for which the following applies.

- Subjects with maximum GCP deviation
- Subjects who received no administrations of the investigational medicinal product
- Subjects without any efficacy related assessment

3.2.4. PPS

Analysis set from FAS excluding subjects for which the following applies.

PPS analysis is performed in order to check the robustness of the results from the FAS analysis.

- Subjects for whom the inclusion criteria do not apply and who meet the exclusion criteria
- Subjects whose administration of the investigational medicinal product does not meet 26 weeks
- Subjects with a drug compliance for the investigational medicinal product that is less than 70%

3.2.5. Safety Analysis Set

Among the registered subjects, this set refers to those who have been administered the investigational medicinal product more than once. However, when an adverse event appears or it is discovered that the case meets the exclusion criteria after being administered the investigational medicinal product, the case shall be included in the analysis set.

3.3. Handling of Missing Values, Outliers and Other

The missing values and outliers as well as the definitive handling during the period in the

analysis are determined until the data is fixed when necessary based on the opinions and feedback from medical specialists. The cases and values excluded from the analysis are included in the summary tables for individual values, but excluded from the calculation for the descriptive statistics, etc.

3.4. Handling of Date Data

When calculating each measurement, data that match the acceptable range shown below are used. Complementing with data outside of the acceptable range, will be examined to determine their acceptability in the clinical conferences. However, when multiple observed values correspond to the same analysis period, the period close to the reference day is used. When the number of days up to the reference day is the same, the observed values farthest from the date are used.

Refer to 1.3 for the acceptable range.

3.5. Handling of Discontinuation Data

The data up to the discontinuation of administration is used in the analysis. However, for adverse events, data to 28 days after the investigational medicinal product has stopped is used in the analysis.

4. Statistical and Analytical Issues

4.1. Adjusting for Covariance

Adjusting for covariance is not performed.

4.2. Interim Analysis

Interim analysis is not performed.

4.3. Multicenter Trial

In this trial, the plan is executed at a total of 13 facilities and collected data on a total of 15 cases. The calculation of the endpoints based on a single facility is not performed because there are few cases per facility. The subject ID numbers in the case summary table and the facility name summary table are created so that the facility for each case can be identified. (Refer to 9.1 for other diagrams and tables)

4.4. Significance Level

The significance level shall be 5% on both sides. In addition, the confidence level when calculating the confidence interval shall be 95%.

4.5. Multiple Comparisons and Multiplicity

Adjusting for multiplicity is not performed in this trial.

4.6. Total and Separate Examinations

In this clinical trial, total cases will be evaluated. Further evaluation will be performed with no L-arginine Co-Administration and L-arginine Co-Administration subjects separately.

4.7. Statistical Method

4.7.1. Summary Statistics

Unless indicated otherwise, the sample size, arithmetic mean, standard deviation, minimum value, median value and maximum value are calculated for continuous values, and the number of digits shown are established as follows.

Arithmetic mean, median value	The last 2 significant digits of the measurement value are rounded and the value is displayed up to the last digit.
Standard deviation	The last three significant digits of the measurement value are rounded and the value is displayed up to the last 2 digits.
Maximum value,	Significant digits of the measurement value.

minimum value	

4.7.2. Frequency Calculation

Unless indicated otherwise, the percentage (%) for the category values is obtained for the aggregation of frequency and the number of cases for analysis. The percentage (%) is rounded to the first decimal place and is displayed up to the one's place.

4.7.3. Confidence Interval for Percentage

Unless indicated otherwise, the confidence interval is assumed to have an accuracy of 95% based on the Clopper-Pearson method as a confidence interval for the percentage.

4.7.4. Logistic Regression Analysis

The following analysis is performed for logistic regression.

- The 100% responder or the 50% responder shall be response variables, and the cases that correspond to those responders are handled as events in the logistic regression model.
- There shall only be one factor specified in each analysis model.
- When the factor is a category value, the odds ratio shows how many times the value is multiplied for the other levels that are not the odds for a specified level. The 95% confidence

interval and the p-value are calculated for that odds ratio. Firth correction is applied when necessary.

- When the factor is a continuous value, the odds ratio shows how many times the value is multiplied when the unit value, which is specified by the factor value, increases. The 95% confidence interval and the p-value are calculated for that odds ratio. Firth correction is applied when necessary.
- The odds ratio and its 95% confidence interval are rounded to the third decimal place and is displayed up to the third decimal place.
- The p-value is rounded to the fifth decimal place and is displayed up to the fourth decimal place. However, when the value is less than 0.0001 before being rounded, the “<0.0001” is displayed.

4.7.5. Aggregation Method

- Aggregating the regimen with and without the co-administration of arginine is performed for the total analysis set, for the regimen with and without co-administration of arginine (Total of 3 types).

- The aggregation is performed in the analysis sets that are established in Chapters 5, 6, 7 and 8. Unless there is no special notation, the aggregation is performed for both with or without the co-administration of arginine in the aggregation and analysis for these chapters.
- Unless there is a special notation for the aggregation before and after the co-administration of arginine as well as before and after the regimen without the co-administration of arginine (2 types for before and after the administration), “Before administration” shall be the “Evaluation period for the stroke-like episode” before starting the clinical trial. “After administration” shall be the “Evaluation period for the stroke-like episode” after starting the clinical trial.
- The definition of the “Evaluation period for the stroke-like episode” for cases without the co-administration of arginine shall be as follows.

  Before starting the clinical trial: 78 weeks before acquiring consent
- After starting the clinical trial: From 9 weeks after starting the administration of the investigational medicinal product until administration is stopped (Period up to the week 8 after starting the administration of the investigational medicinal product does not include the evaluation period).
- The definition of the “Evaluation period for the stroke-like episode” for cases with the co-administration of arginine shall be as follows.

Before starting the clinical trial: Arginine administration period before acquiring consent (after the week 26 and before the week 78).

4.7.6. Software Used

The following software is used.

OS	:	Windows Server 2008
Statistical analysis	:	SAS (Ver. 9.3)

4.7.7. Glossary of Adverse Events

The event names are based on the preferred terms (PT) in the MedDRA code, and the organ names are based on the system organ class (SOC). In addition, Version 17.1 is used for MedDRA.

4.7.8. Drug Name Codes

The drug names use the codes from the data file for medicine names.

5. Trial Subjects

5.1. Breakdown of Subjects and Completion of Trial

5.1.1. Breakdown of Subjects

Analysis Range

Cases with Acquired Consent

Aggregation Table

・ The frequency is aggregated for the cases with acquired consent, the enrolled subjects and the subjects omitted before registration.

In addition, the frequency is aggregated for the FAS, PPS and the safety analysis set(T050101), and the percentage is obtained for the enrolled subjects.Graph

・ The frequency is aggregated for the breakdown of the subjects shown below, and a flow chart is created (F050101).

Breakdown of Subjects	Definitions of Subjects
Cases with acquired consent	-
Enrolled subjects	-
Subjects omitted before registration	Subjects that were not enrolled of the cases whose consent was acquired
Subjects used in safety analysis set	-
Subjects not used in safety analysis set	Subjects that are not used in the safety analysis set from the registered subjects
Subjects used in FAS	-
Subjects not used in FAS	Subjects that are not used in the FAS from the enrolled subjects
Subjects used in PPS	-
Subjects not used in PPS	Subjects from the FAS that were not used in the PPS

Summary Table

・ A table that summarizes the inclusion and exclusion criteria for the subjects that were not enrolled of the cases whose consent were acquired is provided.

5.1.2. Discontinued Cases

Analysis Range

Registered Subjects

Calculation Table

・ The percentage is obtained for the number of completed cases, discontinued cases and cases for analysis. In addition, with regard to the discontinued cases, the percentage of the number of subjects per reason for discontinuation and ratio to the number of cases for analysis (T050102).

Summary Table

・ The administration start date, the discontinuation date and the reason for discontinuing are shown in a summary table for the discontinued cases.

5.2. Deviation from Protocol

Analysis Range

Cases with Acquired Consent

Summary Table

・A summary table shows the reason for deviation for the cases that deviated from the Protocol (L0502).

5.3. Subjects Excluded from Analysis Sets

Summary Table

・The enrolled subjects are analyzed and a summary table is created for subjects excluded from the safety analysis set (L0503).The enrolled subjects are analyzed and a summary table is created for subjects excluded from FAS (L0503).The FAS is analyzed and a summary table is created for subjects excluded from PPS (L0503).Administration Status

Analysis Range

FAS

Aggregation method

- The method for calculating the number of days of administration is: “Days investigational product was taken in previous clinical trial” for week 52 (or when administration was discontinued) – “Number of doses” + 1
- Calculation method for drug compliance (%) is: 100 × (Days of administration × 3 – Times drug was not taken) / (Days of administration × 3). “Times drug was not taken from the previous visit (including times subject forgot and withdrawal) (Times)” shall be used for week 4, week 12, week 24, week 36 and week 52 (or when administration was discontinued) to calculate the “Times drug was not taken.”
- The method for calculating the total dose (g) is: Dose for week 0 (g/day) × (Days of administration × 3 - Times drug was not taken).

Aggregation Table

- The summary statistics (T0504) is obtained for the number of days of administration and the drug compliance (%).

Summary Table

- A summary is created for the administration status (L0504) per case.Patient Background

Analysis Range

FAS, PPS and Safety Analysis Set

Analysis Items

- Gender (Male, Female)
- Age (years old)
- Age (10-<20years old, 20-<30 years old, 30-<40 years old, 40-<50 years old)
- Appearance of stroke-like episodes in the 78 weeks* before acquiring consent (Frequency of appearance is made a category)
- Usage status of arginine intravenous drug (Not used, used)
- Mitochondria DNA point mutation: A3243G (None, present)
- Mitochondria DNA point mutation: T3271C (None, present)
- Mitochondria DNA point mutation: G3244A (None, present)
- Mitochondria DNA point mutation: T3258C (None, present)
- Mitochondria DNA point mutation: T3291C (None, present)
- Systolic pressure (mmHg)
- Diastolic pressure (mmHg)
- Pulse (BPM)
- Height (cm)

・ Weight (kg)

・ Weight (<15 kg, 15-<25 kg, 25-<40 kg, 40 kg -)

・ Complications (None, present)

・ Smoking history (No smoking history, currently smoking and smoked previously)

・ Past medical history in the 78 weeks* before acquiring consent (None, present)

*Usage period for arginine oral drug (after week 26 and before week 78) for subjects who continue to use arginine oral drug

Aggregation Table

・ Summary statistics are obtained for the continuous values of the analysis items. The frequency is aggregated for the category value (T06).

Summary Table

・ A summary of the subject's history is created (T06_01).

・ A summary on the occurrence of stroke-like episodes in the 78 weeks before acquiring consent (Frequency of occurrence is made a category) (T06_02).

・ A summary is created for the mitochondria (T06_05) DNA point mutations.

・ A summary of the height and weight is created.

7. Efficacy Analysis

Analysis Range

FAS

Summary Table

・ The FAS is analyzed and a summary is created for the efficacy (L0701).

・ The FAS is analyzed and a summary is created for the episodes and the occurrence of other symptoms after administration (from administration start day) (L0704).The FAS is analyzed and a summary is created for the episodes and the appearance of other symptoms before administration (from before administration start day) (L0704).Primary Endpoints for Efficacy

(100% Responder Rate)

Analysis Range

FAS and PPS

Aggregation Method

・ The cases without any stroke-like episodes (0 times) during the evaluation period (from week 9 after starting the administration of the investigational product until its administration is completed) shall have a 100% responder rate.

Aggregation Table

・ The frequency of the 100% responder is aggregated and the confidence interval (T0701_01) for the percentage is obtained.Logistic regression analysis is performed with the 100% responder as the response variable. The specified factors as well as the comparison method and units are as follows (T0701_02).

Factor	Comparison / Unit
Gender	Female or male
Age when consent is acquired – years old	+10 years old
Frequency of stroke-like episodes in the 78 weeks* before acquiring consent	+1 time
Complications	None or present
Smoking history	No smoking history or currently smoking
	No smoking history or smoked previously
Past medical history in the 78 weeks* before acquiring consent	None or present
Blood taurine concentration (Week 0)	+100 nmol/mL

Factor	Comparison / Unit
Blood taurine concentration (After week 52 (or when administration was discontinued))	+100 nmol/mL
Blood arginine concentration (Week 0)	+100 nmol/mL
Blood arginine concentration (After week 52 (or when administration was discontinued))	+100 nmol/mL
Mitochondrial DNA mutation rate (Week 0)	+10%
Mitochondrial DNA mutation rate (After week 52 (or when administration was discontinued))	+10%
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 0)	+0.1 folds
$tRNA^{Leu(UUR)}$ taurine modification rate (After week 52 (or when administration was discontinued))	+0.1 folds
ND6 protein level (Week 0)	+10 pg/mL
ND6 protein level (After week 52 (or when administration was discontinued))	+10 pg/mL
Lactic acid in blood (Week 0)	+10 mg/dL

Factor	Comparison / Unit
Lactic acid in blood (After week 52 (or when administration was discontinued))	+10 mg/dL
Lactic acid in CSF (Week 0)	+10 mg/dL
Lactic acid in CSF (After week 52 (or when administration was discontinued))	+10 mg/dL
Pyruvic acid in blood (Week 0)	+0.1 mg/dL
Pyruvic acid in blood (After week 52 (or when administration was discontinued))	+0.1mg/dL
Pyruvic acid in CSF (Week 0)	+0.1 mg/dL
Pyruvic acid in CSF (After week 52 (or when administration was discontinued))	+0.1 mg/dL
Ratio of lactic acid / pyruvic acid in blood (Week 0)	+1
Ratio of lactic acid / pyruvic acid in blood (After week 52 (or when administration was discontinued))	+1
Ratio of lactic acid / pyruvic acid in CSF (Week 0)	+1

Factor	Comparison / Unit
Ratio of lactic acid / pyruvic acid in CSF (After week 52 (or when administration was discontinued))	+1
JMDRS (Week 0)	+10
JMDRS (After week 52 (or when administration was discontinued))	+10

The following subjects are analyzed, and the frequency of the 100% responder is calculated and the confidence interval for the percentage is obtained (T0701_03).

Analysis Subjects
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 78 week period before acquiring consent
Subjects who have at least two local neurological signs (regardless of confirmation of high signal intensity in MRI image of head) in the 78 week period before acquiring consent and subjects who have at least one local neurological sign (confirmed high signal intensity in MRI image of head)
Subjects who have at least two local neurological signs (regardless of confirmation of high signal intensity in MRI image of head) in the 78 week period before acquiring consent

Analysis Subjects
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 52 week period before acquiring consent
Subjects who have at least two local neurological signs (regardless of confirmation of high signal intensity in MRI image of head) in a 52 week period before acquiring consent

7.2. Secondary Endpoints for Efficacy (1) Improvement or Presence of Clinical Symptoms

Analysis Range

FAS and PPS

Aggregation Method

・ In this analysis, a score is aggregated for the regimens with and without the co-administration of arginine during each period, totally and separately (2 types for week 0 and after week 52 (or when administration was discontinued)).

Aggregation Table

- The frequency is aggregated for the score in each section. However, the frequency is aggregated for the score per section when the section details are present. In addition, the summary statistics are calculated for the total score per section and total score overall. The sections, section details and the scores (T0702_01) are as follows.

Section	Section Details	Score
Section1	Speech	0, 1, 2, 3, 4
	Swallowing	0, 1, 2, 3, 4
	Handwriting	0, 1, 2, 3, 4
	Cutting food – Handling utensils (Hand motor skills)	0, 1, 2, 3, 4
	Dressing	0, 1, 2, 3, 4
	Hygiene	0, 1, 2, 3, 4
	Falling	0, 1, 2, 3, 4
	Paroxysmal event (migraine, seizures)	0, 1, 2, 3, 4
Section2	Proximal muscle strength (modified MRC)	0, 1, 2, 3, 4, 5
	Upper limbs coordination	0, 1, 2, 3, 4

Section	Section Details	Score
	Walking	0, 1, 2, 3, 4
	Moderate motor activities (such as vacuum cleaning, carrying groceries, climbing one flight of stairs, preparing your own bed)	0, 1, 2, 3, 4
	Vigorous motor activities (such as running, climbing several flights of stairs or participation on other strenuous sports)	0, 1, 2, 3, 4
Section3:	Vision	0, 1, 2, 3, 4, 5
	Hearing	0, 1, 2, 3, 4
Section4	Endocrine disorder	0, 1, 2, 3
Section5	Cardiac complication	0, 1, 2, 3, 4
Section6	Renal function	0, 1, 2, 3, 4
Section7	Mental retardation	0, 1, 2, 3, 4
	Motivation and drive	0, 1, 2, 3, 4

Summary Table

・ FAS is analyzed and a summary is created for the Section Table 1 for the improvement or persistence of clinical symptoms (Japanese Mitochondrial Disease Rating Scale (JMDRS).

・ FAS is analyzed and a summary is created for the Section Tables 2 and 3 for the improvement or persistence of clinical symptoms (JMDRS) (L0702_01).

・ FAS is analyzed and a summary is created for the Section Tables 4 to 7 for the improvement or persistence of clinical symptoms (JMDRS) (L0702_01).Secondary Endpoints for Efficacy

(2) 50% Responder Rate

Analysis Range

FAS and PPS

Calculation Method

・ The 50% responders are cases showing a decrease of more than 50% in the number of stroke-like episodes over 4 weeks during the evaluation period after administering the investigational product when compared to before its administration.

Calculation Table

・ The frequency of the 50% responder is aggregated and the confidence interval for the percentage is obtained (T0702_02).Logistic regression analysis is performed with the 50% responder as the response variable. The specified factor, comparison method and unit (T0701_02) shall be the same as the primary endpoints (100% responder).

7.4. Secondary Endpoints for Efficacy (3) Frequency of Abrupt-onset Focal Neurological Deficits (Regardless of Confirmation of High Signal Intensity in MRI Diffusion Weighted Image of Head) During Episode Based on MELAS Stroke Assessment Criteria

Analysis Object

FAS and PPS

Aggregation Method

・ In this analysis, the appearance of signs is calculated for the regimens with and without the co-administration of arginine before and after administration, totally and separately (2 types for before and after administration).

・ The incidence rate is the number of episodes that is averaged out per month during the observation period (month). Note that one month is equal to 28 days.

Calculation Table

・ The frequency is aggregated as a category for the number of appearances collected in the data. In addition, the summary statistics(T0702_03) are obtained for the incidence rate, and the number of digits is established for showing the valid digits of the incidence rate, which is rounded to the second decimal place (including the second decimal place).

7.5. Secondary Endpoints for Efficacy (4) Special Examination

Analysis Range

FAS and PPS

Calculation Method

- In this analysis, data is aggregated in a special examination for the regimens with and without the co-administration of arginine during each period, totally and separately (2 types for week 0 and after week 52 (or when administration was discontinued)). The rate of change (%) in this analysis is the corresponding analysis set, which applies to the subjects without missing values in week 0 and after week 52 (or when administration was discontinued), and it is calculated using the following formula.

$$100 \times \frac{\text{Value for after week 52 (or when administration was discontinued)} - \text{Value for week 0}}{\text{Value for week 0}}$$

- The “Blood lactic acid / pyruvic acid ratio” is calculated by dividing the lactic acid in blood by pyruvic acid in blood. To calculate the summary statistics, the number of significant digits for this value is rounded to the tenths place (including the tenths place). In the same way, the method for calculating “Ratio of lactic acid / pyruvic acid in CSF” is calculated by dividing the lactic acid in CSF by pyruvic acid in CSF. To calculate the summary statistics, the number of significant digits for this value is rounded to the tenths place (including the tenths place).

・ The number of days is calculated as follows: (Date of blood sampling or date of CSF collection) – Start date for administration of investigational product.

Aggregation Table

・ The summary statistics are calculated for the special examinations noted below. In addition, the summary statistics are obtained for the rate of change between the regimens with and without the co-administration of arginine. The number of significant digits for the rate of change (%) is rounded to the tenths place (including the tenths place) (T0702_04).

Special Examination
Lactic acid in blood
Lactic acid in CSF
Pyruvic acid in blood
Pyruvic acid in CSF
Ratio of lactic acid / pyruvic acid in blood
Ratio of lactic acid / pyruvic acid in CSF
Taurine concentration in blood
Taurine concentration in CSF

Graph

- A trend diagram is created for the FAS with the taurine in the blood and the arginine in the blood on the vertical axis and the number of days on the horizontal axis (G0702_04).
- A trend diagram is created for the FAS with the taurine in the CSF and the arginine in the CSF on the vertical axis and the number of days on the horizontal axis (G0702_04).
- A trend diagram is created for the FAS with the special examination values noted below on the vertical axis and the number of days on the horizontal axis (G0702_05).

Special Examination
Lactic acid in blood
Pyruvic acid in blood
Ratio of lactic acid / pyruvic acid in blood
Lactic acid in CSF
Pyruvic acid in CSF
Ratio of lactic acid / pyruvic acid in CSF
Mitochondrial DNA mutation rate
$tRNA^{Leu(UUR)}$ taurine modification rate
ND6 protein level

Summary Table

・ The FAS is analyzed and a summary is created for the special examinations (L0702_04).

7.6. Secondary Endpoints for Efficacy (5) Imaging Scan (MRI Scan of Head)

Analysis Range

FAS and PPS

Aggregation Method

・ In the shift table, the frequency is aggregated combining the imaging test results (also including the total) for week 0 and after week 52 (or when administration was discontinued).

・ When both types of abnormalities (from the high signal check and other) are selected, it is counted as abnormalities from the high signal check.

Aggregation Table

・ A shift table is created for the imaging scan results (T0702_05_a) from the diffusion-weighted image (axial) noted below.

・ A shift table is created for the other imaging scan results besides the diffusion-weighted image (axial) noted below (T0702_05_b).

Imaging Scan	Imaging Scan Results
Diffusion weighted image (axial)	Normal, abnormal (confirmed high signal intensity), abnormal (other), not taken
MRA image (intracranial)	Normal, abnormal, not taken
FLAIR image (axial)	Normal, abnormal, not taken
T2 weighted image (axial)	Normal, abnormal, not taken
T1 weighted image (axial)	Normal, abnormal, not taken
T2* weighted image (axial)	Normal, abnormal, not taken
ADC map	Normal, abnormal, not taken

Summary Table

・ The FAS is analyzed and a summary is created for the imaging scans (L0702_05_01, L0702_05_02).

7.7. Secondary Endpoints for Efficacy (6) Times Arginine Intravenous Drug Was Used Before and After the Administration of the Investigational Product

Analysis Range

FAS and PPS

Calculation Method

- In this analysis, the frequency of administration is aggregated for the regimens with and without the co-administration of arginine before and after administration (2 types for before and after administration).
- The abovementioned aggregation is performed when the episode definition is not referenced using the MRI high signal check and when the MRI high signal check is referenced.

Aggregation Table

- The frequency is aggregated as a category for the extended frequency of administration collected in the data.

  In addition, the frequency of administration per one episode by finding the frequency aggregation and ratio to the total number of episodes.

Summary Table

- The FAS is analyzed and a summary is created for the usage status of the arginine intravenous drug before and after the administration of the investigational product.Secondary Endpoints for Efficacy (7) Number of Confirmed High Intensity Signals When MRI of Head is Conducted After Subject Suffers from Headaches, Nausea, Vomiting, Convulsions and Disorder of Consciousness

Analysis Range

FAS and PPS

Calculation Table

- The frequency is calculated as a category for the number of high signal intensity checks collected in the data (T0702_07).MMSE (Mini-Mental State Examination) Score

Analysis Range

FAS and PPS

Calculation Method

- In this analysis, an MMSE score is calculated for the regimens with the total subjects. It is further calculated for the regimens with and without the co-administration of arginine during

each period separately (2 types for week 0 and week 52 (or when administration was discontinued).

Calculation Table

・ The frequency is calculated for the MMSE score noted below. In addition, the summary statistics are calculated for the MMSE score total. The MMSE scores and the corresponding categories are as follows (T0703).

MMSE Score	Score Category
Time orientation	0, 1, 2, 3, 4, 5
Location orientation	0, 1, 2, 3, 4, 5
Immediate recall	0, 1, 2, 3
Calculation	0, 1, 2, 3, 4, 5
Delayed recall	0, 1, 2, 3
Naming of objects	0, 1, 2
Sentence repetition	0, 1
Oral instructions	0, 1, 2, 3
Written instructions	0, 1
Spontaneous writing	0, 1

MMSE Score	Score Category
Figure imitation	0, 1

Summary Table

- The FAS is analyzed and a summary is created for the MMSE score.

8. Safety Analysis

8.1. Adverse Events

Analysis Range

Safety Analysis Set

Calculation Method

- Adverse events are calculated when they appear after the administration of the investigational product has started and up to a period of 28 days after it has stopped being administered.
- The adverse event names are codified using the MedDRA, the preferred terms (PT) based on the MedDRA code are used, and the organ names are used based on the system organ class (SOC).
- The events that appear after the investigational product administration has started are handled as adverse events. Among the adverse events, those events whose causal relationship with the

investigational product cannot be denied (“1. Clearly relationship,” “2. Possible relationship” and “Relationship cannot be denied”) are handled as adverse reactions.

- In the calculation for severity classification, when multiple adverse events are observed in the same subject, the most severe adverse event is counted.
- In the aggregation by SOC and by severity classification, when multiple adverse events (or adverse reactions) are observed for the same subject and same SOC, the most severe adverse event (or adverse reaction) will be counted.
- In the aggregation for classifying the relationship with the investigational product, when multiple adverse events are observed in the same subject and their relationship with the investigational product is mixed with “Related” (adverse reaction) and “Unrelated” (adverse events that are not adverse reactions), the result is counted as “Related.”

Calculation Table

- The frequency (T080101_01) for the number of appearances is calculated for the following items and the adverse events are summarized.

Item
All adverse events
Serious adverse event

Item
Fatal case
Adverse event causing discontinuation
Severity (Mild, moderate and serious)
Relationship with investigational medicinal product (None, present)

- The frequency is aggregated for all adverse events and for adverse events by SOC, by PT and by severity (T080101_02). In addition, the frequency is aggregated for adverse events by SOC and by PT.

Summary Table

- A summary of the adverse events is created (L080101).
- A summary of the fatalities is created (L080101).
- A summary of the serious adverse events is created (L080101).
- A summary of the adverse events causing discontinuation is created. (L080101).

8.2. Clinical Examination

Analysis Object

Safety Analysis Set

Aggregation Method

・ In this analysis, the values in the clinical examination are aggregated for the regimens with and without the co-administration of arginine during each period (6 types for week 0, after week 4, after week 12, after week 24, after week 36 and after week 52 (or when administration was discontinued)).

・ Calculation Table

・ The summary statistics are calculated for the hematological tests (in-hospital) noted below (T080102).

Hematological Test (In-hospital)
RBC count
WBC count
Blood platelet count
Hemoglobin content
Hematocrit level
Neutrophils
Lymphocytes

・ The summary statistics are calculated for the biochemical tests (in-hospital) noted below (T080102).

Biochemical Test (In-hospital)
Total protein
Albumin
Glucose
HbA1c value
AST (GOT)
ALT (GPT)
ALP
LDH
γ-GTP
CK
T-Bil
D-Bil
BUN
Cre

Biochemical Test (In-hospital)
eGFR
Uric acid
TG
T-Cho
Na
K
Cl

Graph

- A trend diagram is created with the hematological test on the vertical axis and with the number of days on the horizontal axis (G080101).
- A trend diagram is created with the biochemical test on the vertical axis and with the number of days on the horizontal axis (G080101).

Summary Table

- A summary of the in-hospital blood test and hematological test is prepared (L080102_01).A summary of the in-hospital biochemical tests is prepared (L080102_01).
- Special examination and blood test: Summary of blood amino acid analyses (39 types) is prepared (L080102_02)

・ Special examination and CSF test: Summary of CSF amino acid analyses (39 types) is prepared (L080102_02).

・ Special examination and WBC test: Summary (Measurements from Kawasaki Medical School, Nippon Medical School – Institute of Gerontology) for the WBC [Voluntary test] is prepared.

8.3. Physical Examination

Analysis Object

Safety Analysis Set

Calculation Method

・ In this analysis, the values in the physical examination are calculated during each period (6 types for week 0, after week 4, after week 12, after week 24, after week 36 and after week 52 (or when administration was discontinued)).

・ Aggregation Table

・ The summary statistics are obtained for the physical examination noted below (T080103).

Physical Examination
Systolic pressure

Physical Examination
Diastolic pressure
Pulse
Weight
Body temperature

Graph

・ A trend diagram is created with the physical examination on the vertical axis and with the number of days on the horizontal axis (G080103).

Summary Table

・ A summary of the physical examination is created.

9. Appendix

9.1. Other Diagrams and Charts

Summary Table

・ The safety analysis set (L0901_01) is analyzed, and a summary of the past medical history is created.

- The safety analysis set is analyzed, and a summary of the complications is created. (L0901_02).
- The safety analysis set is analyzed, and a summary of the concomitant drugs is created (L0901_03).The safety analysis set is analyzed, and a summary of the concomitant treatments is created (L0901_04).
- The cases with acquired consent (L0901_05) are analyzed, and a summary is created for cases that are accepted or rejected.

Summaries of Changes to the Statistical Analysis Plan

<table>
<tr><th>Item</th><th>Before Revision</th><th>After Revision</th><th>Reason for Revision</th></tr>
<tr><td>Prepared on</td><td>10/7/2014</td><td>2/2/2015</td><td>Version revision.</td></tr>
<tr><td>Version No.</td><td>Ver. 1.0</td><td>Ver. 1.1</td><td>Version revision.</td></tr>
<tr><td>Revision History</td><td>
<table>
<tr><th>Ver.</th><th>Effective Date</th><th>Prepared/ Revised by</th><th>Change Log</th></tr>
<tr><td>1.0</td><td>2014/10/7</td><td>Kazuhiro Saito</td><td>Created new document.</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
</td><td>
<table>
<tr><th>Ver.</th><th>Effective Date</th><th>Prepared/ Revised by</th><th>Change Log</th></tr>
<tr><td>1.0</td><td>2014/10/7</td><td>Kazuhiro Saito</td><td>Created new document.</td></tr>
<tr><td>1.1</td><td>2015/2/2</td><td>Kazuhiro Saito</td><td>Unified notation and clarified definitions.</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
</td><td>Version revision.</td></tr>
<tr><td>4.7.5 Aggregation Method</td><td>No notation</td><td>・ Unless there is a special notation for the aggregation before and after the co-administration of arginine as well as before and after the regimen without the co-administration of arginine (2 types for before and after the administration), “Before administration” shall be the “Evaluation period for the stroke-like episode” before starting the clinical trial. “After administration” shall be the “Evaluation period for the stroke-like episode” after starting the clinical trial.
・ The definition of the “Evaluation period for the stroke-like episode” for cases without the co-administration of arginine shall be as follows. Before starting the clinical trial: 78 weeks before acquiring consent.
・ After starting the clinical trial: From 9 weeks after starting the administration of the investigational medicinal product until administration is stopped (Period up to the week 8 after starting the administration of the investigational medicinal product does not include the evaluation period).
・ The definition of the “Evaluation period for the stroke-like episode” for cases with the co-administration of arginine shall be as follows. Before starting the clinical trial: Arginine administration period before acquiring consent (after the week 26 and before the week 78).</td><td>Clarified definitions.</td></tr>
<tr><td>4.7.6. Software Used</td><td>Windows 7</td><td>Windows Server 2008</td><td>Changed operating system.</td></tr>
<tr><td>5.4. Administration Status</td><td>Aggregation method
・No notion</td><td>Aggregation method
・ The method for calculating the number of days of administration is: “Days investigational product was taken in previous clinical trial” for week 52 (or when administration was discontinued) – “Number of doses” + 1
・ Calculation method for drug compliance (%) is:</td><td>Clarified definitions.</td></tr>
</table>

		100 × (Days of administration × 3 – Times drug was not taken) / (Days of administration × 3). "Times drug was not taken from the previous visit (including times subject forgot and withdrawal) (Times)" shall be used for week 4, week 12, week 24, week 36 and week 52 (or when administration was discontinued) to calculate the "Times drug was not taken." ・ The method for calculating the total dose (g) is: Dose for week 0 (g/day) × (Days of administration × 3 - Times drug was not taken).	
7. Efficacy Analysis	・ The FAS is analyzed and a summary is created for the episodes and the occurrence of other symptoms after administration（L0704）. ・ The FAS is analyzed and a summary is created for the episodes and the appearance of other symptoms before administration（L0704）.	・ The FAS is analyzed and a summary is created for the episodes and the occurrence of other symptoms after administration (from administration start day)（L0704）. ・ The FAS is analyzed and a summary is created for the episodes and the appearance of other symptoms before administration (from before administration start day)（L0704）.	Added summary list for before administration and clarified definitions.
7.1. Primary Endpoints for Efficacy (100% Responder Rate)	Taurine blood concentration (Week 0) Taurine blood concentration (Week 52) Arginine blood concentration (Week 0) Arginine blood concentration (Week 52) Mitochondrial DNA mutation rate (Week 52) $tRNA^{Leu(UUR)}$ taurine modification rate (Week 52) ND6 protein level (Week 52) Lactic acid in blood (Week 52) Lactic acid in CSF (Week 52) Pyruvic acid in blood (Week 52) Pyruvic acid in CSF (Week 52) Ratio of lactic acid and pyruvic acid in blood (Week 52) Ratio of lactic acid and pyruvic acid in CSF (Week 52) JMDRS (Week 52)	Blood taurine concentration (Week 0) Blood taurine concentration (After week 52 (or when administration was discontinued)) Blood arginine concentration (Week 0) Blood arginine concentration (After week 52 (or when administration was discontinued)) Mitochondrial DNA mutation rate (After week 52 (or when administration was discontinued)) $tRNA^{Leu(UUR)}$ taurine modification rate (After week 52 (or when administration was discontinued)) ND6 protein level (After week 52 (or when administration was discontinued)) Lactic acid in blood (After week 52 (or when administration was discontinued)) Lactic acid in CSF (After week 52 (or when administration was discontinued)) Pyruvic acid in blood (After week 52 (or when administration was discontinued)) Pyruvic acid in CSF (After week 52 (or when administration was discontinued)) Ratio of lactic acid / pyruvic acid in blood (After week 52 (or when administration was discontinued)) Ratio of lactic acid / pyruvic acid in CSF (After week 52 (or when administration was discontinued))	Corrected error.

		JMDRS (After week 52 (or when administration was discontinued))	
7.2. Secondary Endpoints for Efficacy (1) Improvement or Presence of Clinical Symptoms	Aggregation Method In this analysis, a score is aggregated for the regimens with and without the co-administration of arginine during each period, totally and separately (2 types for week 0 and week 52).	Aggregation Method In this analysis, a score is aggregated for the regimens with and without the co-administration of arginine during each period, totally and separately (2 types for week 0 and after week 52 (or when administration was discontinued)).	Corrected error.
7.4. Secondary Endpoints for Efficacy (3) Frequency of Sudden Local Neurological Signs (Regardless of Confirmation of High Signal Intensity in MRI Diffusion Weighted Image of Head) During Episode Based on MELAS Stroke Assessment Criteria	The incidence rate is the number of episodes that is averaged out per month during the extended observation period (month). Note that one month is equal to 28 days. In addition, the number of extended observation days is aggregated as follows: Final observation day for week 52 (or when administration was discontinued) – Administration start day + 1.	The incidence rate is the number of episodes that is averaged out per month during the observation period (month). Note that one month is equal to 28 days.	Clarified definitions.
7.5. Secondary Endpoints for Efficacy (4) Special Examination	In this analysis, data is aggregated in a special examination for the regimens with and without the co-administration of arginine during each period, totally and separately (2 types for week 0 and week 52 (or when administration was discontinued)). The rate of change (%) in this analysis is the corresponding analysis set, which applies to the subjects without missing values in week 0 and week 52 (or when administration was discontinued), and it is calculated using the following formula. $100 \times \frac{\text{Value for week 52 (or when administration was discontinued)} - \text{Value for week 0}}{\text{Value for week 0}}$	In this analysis, data is aggregated in a special examination for the regimens with and without the co-administration of arginine during each period, totally and separately (2 types for week 0 and after week 52 (or when administration was discontinued)). The rate of change (%) in this analysis is the corresponding analysis set, which applies to the subjects without missing values in week 0 and after week 52 (or when administration was discontinued), and it is calculated using the following formula. $100 \times \frac{\text{Value for after week 52 (or when administration was discontinued)} - \text{Value for week 0}}{\text{Value for week 0}}$	Corrected error.
7.5. Secondary Endpoints for Efficacy (4) Special Examination	No notation	・ The “Blood lactic acid/ pyruvic acid ratio” is calculated by dividing the lactic acid in blood by pyruvic acid in blood. To calculate the summary statistics, the number of significant digits for this value is rounded to the tenths place (including the tenths place). In the same way, the method for calculating “Ratio of lactic acid / pyruvic acid in CSF” is calculated by dividing the lactic acid in CSF by pyruvic acid in CSF. To calculate the summary statistics, the number of significant digits for this value is rounded to the tenths place (including the tenths place). ・ The number of days is calculated as follows: (Date of blood sampling or date of CSF collection) –	Clarified definitions.

<table>
<tr><td></td><td></td><td>Start date for administration of investigational product.</td><td></td></tr>
<tr><td>7.5. Secondary Endpoints for Efficacy (4) Special Examination</td><td><table><tr><th>Special Examination</th></tr><tr><td>Lactic acid level in blood</td></tr><tr><td>Lactic acid level in CSF</td></tr><tr><td>Pyruvic acid level in blood</td></tr><tr><td>Pyruvic acid level in CSF</td></tr><tr><td>Ratio of lactic acid and pyruvic acid in blood</td></tr><tr><td>Ratio of lactic acid and pyruvic acid in CSF</td></tr><tr><td>Taurine level in blood</td></tr><tr><td>Taurine level in CSF</td></tr></table></td><td><table><tr><th>Special Examination</th></tr><tr><td>Lactic acid in blood</td></tr><tr><td>Lactic acid in CSF</td></tr><tr><td>Pyruvic acid in blood</td></tr><tr><td>Pyruvic acid in CSF</td></tr><tr><td>Ratio of lactic acid / pyruvic acid in blood</td></tr><tr><td>Ratio of lactic acid / pyruvic acid in CSF</td></tr><tr><td>Taurine concentration in blood</td></tr><tr><td>Taurine concentration in CSF</td></tr></table></td><td>Corrected error.</td></tr>
<tr><td>7.5. Secondary Endpoints for Efficacy (4) Special Examination</td><td>・ A trend diagram is created for the FAS with the taurine in the blood and the arginine concentration on the vertical axis and the number of days on the horizontal axis (G0702_04).
・ A trend diagram is created for the FAS with the taurine in the CSF and the arginine concentration on the vertical axis and the number of days on the horizontal axis (G0702_04).</td><td>・ A trend diagram is created for the FAS with the taurine in the blood and the arginine in the blood on the vertical axis and the number of days on the horizontal axis (G0702_04).
・ A trend diagram is created for the FAS with the taurine in the CSF and the arginine in the CSF on the vertical axis and the number of days on the horizontal axis (G0702_04)</td><td>Corrected error.</td></tr>
<tr><td>7.5. Secondary Endpoints for Efficacy (4) Special Examination</td><td><table><tr><th>Special Examination</th></tr><tr><td>Lactic acid level in blood</td></tr><tr><td>Pyruvic acid level in blood</td></tr><tr><td>Ratio of lactic acid and pyruvic acid in blood</td></tr><tr><td>Lactic acid value in CSF</td></tr><tr><td>Pyruvic acid value in CSF</td></tr><tr><td>Ratio of lactic acid and pyruvic acid in CSF</td></tr></table></td><td><table><tr><th>Special Examination</th></tr><tr><td>Lactic acid in blood</td></tr><tr><td>Pyruvic acid in blood</td></tr><tr><td>Ratio of lactic acid / pyruvic acid in blood</td></tr><tr><td>Lactic acid in CSF</td></tr><tr><td>Pyruvic acid in CSF</td></tr><tr><td>Ratio of lactic acid / pyruvic acid in CSF</td></tr></table></td><td>Corrected error.</td></tr>
<tr><td>7.6. Secondary Endpoints for Efficacy (5) Imaging Scan (MRI Scan of Head)</td><td>This analysis includes the corresponding analysis set, which applies to the subjects without missing imaging test results in week 0 and week 52 (or when administration was discontinued).
In the shift table, the frequency is aggregated combining the imaging test results (also including the total) for week 0 and week 52 (or when administration was discontinued).</td><td>No notation.

In the shift table, the frequency is aggregated combining the imaging test results (also including the total) for week 0 and after week 52 (or when administration was discontinued).
When both types of abnormalities (from the high signal check and other) are selected, it is counted as abnormalities from the high signal check.</td><td>Corrected because absent values were also included in the aggregation. Clarified definitions.</td></tr>
<tr><td>7.7. Secondary Endpoints for Efficacy (6) Times Arginine Intravenous Drug Was Used Before and After the Administration of the Investigational Product</td><td>The abovementioned aggregation is performed when the episode definition is not referenced using the MRI check and when the MRI check is referenced.</td><td>The abovementioned aggregation is performed when the episode definition is not referenced using the MRI high signal check and when the MRI high signal check is referenced.</td><td>Clarified definitions.</td></tr>
<tr><td>8.1. Adverse Events</td><td>In the aggregation by SOC, by PT and by severity</td><td>In the aggregation by SOC and by severity</td><td>Clarified</td></tr>
</table>

	classification, when multiple adverse events (or adverse reactions) are observed for the same subject, same SOC and same PT, the most severe adverse event (or adverse reaction) will be counted. In the aggregation for classifying the relationship with the investigational product, when multiple adverse events are observed in the same subject and their relationship with the investigational product is mixed with "Related" and "Unrelated," the result is counted as "Related."	classification, when multiple adverse events (or adverse reactions) are observed for the same subject and same SOC, the most severe adverse event (or adverse reaction) will be counted. In the aggregation for classifying the relationship with the investigational product, when multiple adverse events are observed in the same subject and their relationship with the investigational product is mixed with "Related" (adverse reaction) and "Unrelated" (adverse events that are not adverse reactions), the result is counted as "Related."	definitions.
8.1. Adverse Events	The frequency is aggregated for all adverse events and for adverse events by SOC, by PT and by severity (T080101_02).	The frequency is aggregated for all adverse events and for adverse events by SOC, by PT and by severity (T080101_02). In addition, the frequency is aggregated for adverse reactions by SOC and by PT.	Added the aggregation that combines severity.
8.2 Clinical Examination	・ In this analysis, the values in the clinical examination are aggregated for the regimens with and without the co-administration of arginine during each period (6 types for week 0, week 4, week 12, week 24, week 36 and week 52 (or when administration was discontinued)).	・ In this analysis, the values in the clinical examination are aggregated for the regimens with and without the co-administration of arginine during each period (6 types for week 0, after week 4, after week 12, after week 24, after week 36 and after week 52 (or when administration was discontinued)).	Corrected error.
8.2 Clinical Examination	・ A summary of hematological tests (in-hospital) is prepared (L080102_01). ・ A summary of biochemical tests (in-hospital) is prepared (L080102_01). ・ A summary of blood amino acid analyses (39 types) for the blood test (SRL measurement) is prepared (L080102_02). ・ A summary of CSF amino acid analyses (39 types) for the CSF test [Given test] (SRL measurement) is prepared (L080102_02). ・ A summary (Measurements from Kawasaki Medical School, Nippon Medical School – Institute of Gerontology) for the WBC [Voluntary test] is prepared.	・ A summary of the in-hospital blood test and hematological test is prepared（L080102_01）. ・ A summary of the in-hospital biochemical tests is prepared (L080102_01). ・ Special examination and blood test: Summary of blood amino acid analyses (39 types) is prepared (L080102_02). ・ Special examination and CSF test: Summary of CSF amino acid analyses (39 types) are prepared (L080102_02). ・ Special examination and WBC test: Summary (Measurements from Kawasaki Medical School, Nippon Medical School – Institute of Gerontology) for the WBC [Voluntary test] is prepared.	Corrected error.
8.3 Physical Examination	In this analysis, the values in the physical examination are calculated during each period (6 types for week 0, week 4, week 12, week 24, week 36 and week 52 (when administration was discontinued)).	In this analysis, the values in the physical examination are calculated during each period (6 types for week 0, after week 4, after week 12, after week 24, after week 36 and after week 52 (when administration was discontinued)).	Corrected error.

KN01 Multicenter Trial Focusing on

Mitochondrial Encephalomyopathy (MELAS)

Clinical Trial Report
(Efficacy and Safety)

Coordinating Investigator

Kawasaki Medical School

Department of Neurology

Sunada Yoshihide

Date of Creation: 3/26/2015

Clinical Trial Report Number: KN01-MELAS-01

Version Number: Version 1.0

1. Table of Contents

2. Overview

Results:

(Breakdown of Subjects)

・All 10 cases registered were administered the investigational drug and completed this trial. Details of the subjects are shown in Table 4.1.1-5.

(Efficacy Results)

・The 100% responder rate was 60.0% (6/10 subjects, 95% confidence interval: 26.2 to 87.8) in total cases, 100.0% (1/1 subject, 95% confidence interval: 2.5 to 100.0) with no L-arginine Co- Administration case, and 55.6% (5/9 subjects, 95% confidence interval: 21.2 to 86.3) in L-arginine Co-Administration cases.

・The average total JMDRS score increased from 15.2±6.7 at Week 0 to 17.0±9.2 at Week 52 (or when canceled).

・The 50% responder rate was 80.0% (8/10 subjects, 95% confidence interval: 44.4 to 97.5) in total cases, 100.0% (1/1 subject, 95% confidence interval: 2.5 to 100.0) with no L-arginine Co- administration case, and 77.8% (7/9 subjects, 95% confidence interval: 40.0 to 97.2) in L-arginine Co-Administration cases.

・The number of abrupt-onset focal neurological deficits defined in the MELAS stroke diagnostic criteria was more than 2 in total cases before administration of the investigational drug. Abrupt-onset focal neurological deficits were completely prevented in 4 subjects after the administration of the investigational drug. One episode was observed in the remaining 6 cases, respectively.

・At Week 0 and Week 52 (or when canceled) of investigational drug administration, there was no marked change in lactic acid value, pyruvic acid value, and lactic acid to pyruvic acid ratio in the blood and the CSF.

・After Week 52 (or when canceled) of investigational drug administration, new abnormalities were confirmed in head MRI laboratory findings 6 times in 4 subjects [2 cases of diffusion weighted images (axial), 3 cases of T1 weighted images (axial), and 1 case of ADC map (axial)]. Among them, 2 cases of diffusion weighted images (axial) and 2 cases of T1 weighted images (axial) were in the same case.

・The use of L-arginine intravenous preparation was judged by each investigator when abrupt-onset focal neurological deficits occurs without confirmation of the MRI abnormality. Before investigational drug administration, the number of uses of L-arginine intravenous preparation per one episode (total 30 episodes) was 14 (1 case), 13 (1 case), 12 (1 case), 9 (1 case), 8 (3 cases), 7 (1 case), 4 (1 case), 2 (4 cases), 1 (5 cases), 0 (12 cases); after administration, of the number of uses per episodes (total 6 episodes) was 7 (1 case), 2 (1 case), 1 (1 case), and 0 (3 cases). Similar results were observed with confirmation of the MRI abnormality.

・Symptoms other than abrupt-onset focal neurological deficits defined in the MELAS stroke

diagnostic criteria were observed after investigational drug administration twice in 2 cases, among which a high signal was confirmed once in 1 case.

・The rate of taurine modification of mitochondrial $tRNA^{Leu(UUR)}$ in peripheral blood leukocytes increased from Week 0 to Week 52 (or when canceled) in 5 cases out of 9 cases.

Complete disappearance of stroke-like episodes, the primary endpoint, was achieved in 6 out of 10 cases. The lower limit of the 95% confidence interval was 26.2% in total cases and 21.1% in L-arginine Co-Administration cases, which was significantly higher than the threshold responder rate set in the trial protocol. The 50% responder rate also showed a high value of 80%. The frequency of occurrence of abrupt-onset focal neurological deficits as well as the number of usages of L-arginine intravenous preparation decreased, and a significant increase was observed in the rate of $tRNA^{Leu(UUR)}$ modification in peripheral blood leukocytes at Week 52 (or when canceled) of investigational drug administration. From these results, the effectiveness of the investigational drug was demonstrated.

(Safety Results)

・Adverse events occurred in all the cases. No deaths were observed. Serious adverse events occurred twice in 2 cases. Among them, 1 time in 1 case was an increase in blood creatine phosphokinase and gastroenteritis. Adverse events judged as severe and adverse events leading to discontinuation were not observed.

・Adverse events that occurred in 2 cases or more included 5 cases of nasopharyngitis, 4 cases of diarrhea, 3 cases of increased blood creatine phosphokinase, and 2 cases each of leukocytosis, earache, vomiting, fever, influenza, contusion, Increase in C-reactive protein, increase in γ-glutamyl transferase, and increase in the number of neutrophils.

・Side effects included 1 case each of constipation, diarrhea, gastroesophageal reflux disease, hiatal hernia, stomatitis, gastroenteritis, increase in γ-glutamyl transferase, decreased appetite, insomnia, and frequent urination.

・Adverse events judged to be moderate included 2 cases of nasopharyngitis, and 1 case each of earache, vomiting, fever, gingivitis, shingles, increased blood creatine phosphokinase, increased C-reactive protein, increased blood lactate dehydrogenase, arthritis, post herpetic neuralgia, and inflammation of the upper respiratory tract. All remaining adverse events were judged to be mild, and there were no adverse events judged as severe.

・Serious adverse events occurred twice in 2 subjects. Specifically, increased blood creatine phosphokinase and gastroenteritis each occurred once in one case, respectively. Both of them were judged not to be related to the investigational drug. No adverse event occurred that resulted in discontinuation of administration.

(Conclusion)

In terms of effectiveness, the percentage of total cases (100% responder rate) in which the number of abrupt-onset focal neurological deficits confirmed by head MRI abnormalities after investigational drug administration was 0 was 60% (6/10 subjects, 95% confidence

interval: 26.2 to 87.8); it was thus confirmed that stroke-like attacks were suppressed by investigational drug administration.

In terms of safety, serious adverse events suspected to be associated with the investigational drug and adverse events leading to discontinuation were not observed, the adverse events that displayed were mild or moderate, and no severe adverse events were observed.

The above findings validated the effectiveness and safety of taurine as a treatment for suppressing the recurrence of stroke-like attacks in MELAS patients.

3. Clinical Trial Subjects

3.1. Breakdown of Cases

The breakdown of cases is as shown in Figure 1. In this trial, cases of discontinuation were not observed (Table 4.1-2).

Ten cases (with no arginine Co-Administration: 1 case; with arginine Co-Administration: 9 cases) were registered, and all the cases completed the clinical trial.

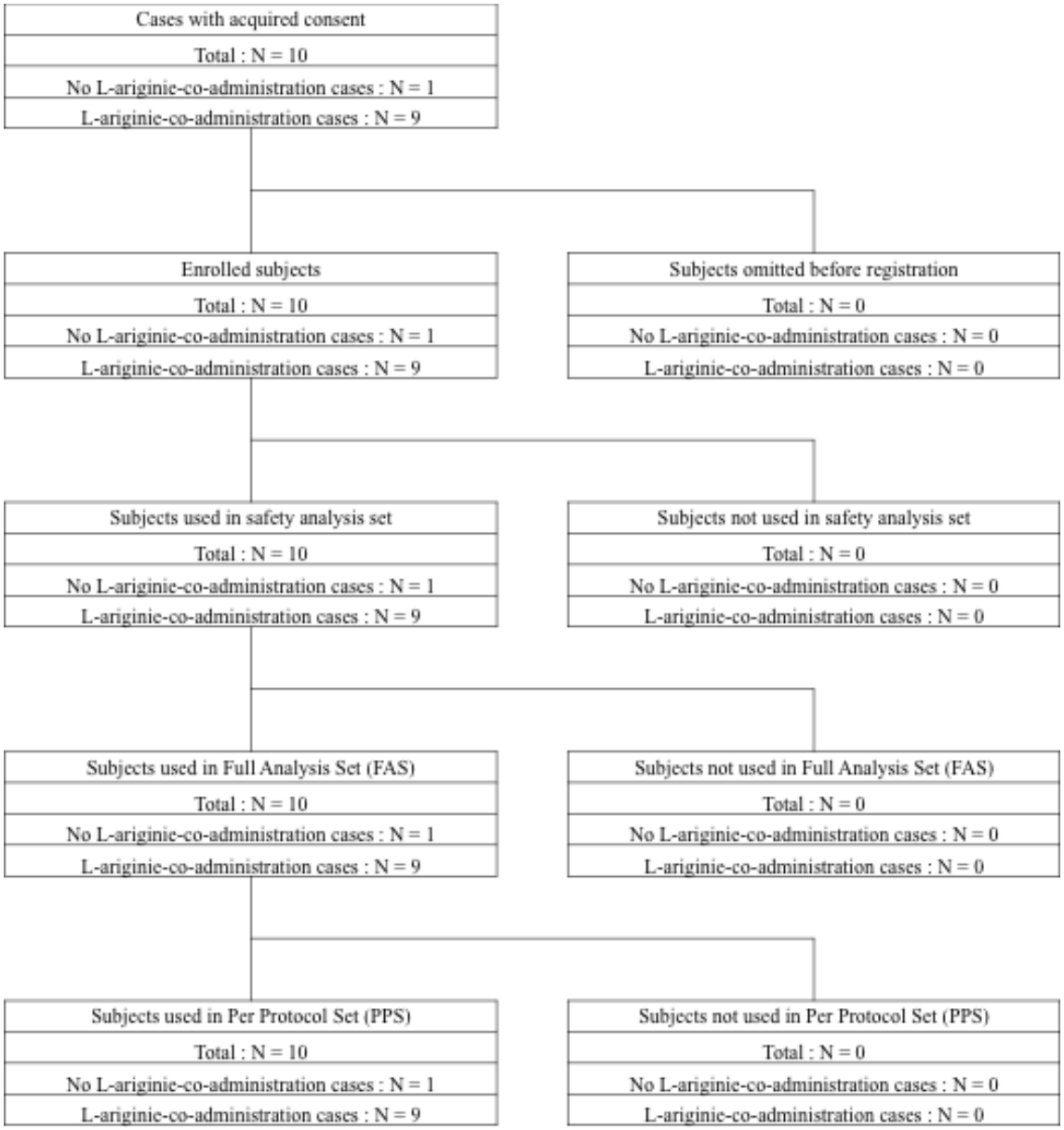

Figure 1 Breakdown of Cases

3.2. Deviations from the Protocol

The protocol stated measurement of ND6 protein amounts in the optional laboratory test was to be measured using blood leukocytes, but all the cases were measured using plasma as well. No

explanation was given to the subjects in advance to the effect that measurement would be conducted on another specimen different from that stated in the original protocol. One case did not consent to measurement of ND6 protein amount; personnel explained the circumstances all subjects including this subject, apologized, and discarded the measurement records for plasma for all subjects.

Table 1 shows other deviations from the protocol.

There were five deviations from the protocol, including 2 cases of subjects who were not inspected at Week 0 as specified, 1 case of failure to conduct a head MRI examination within 2 weeks after a stroke-like attack and a deviation from the MRI Imaging Conditions Confirmation Form, 1 case of noncompliance for taking the investigational drug, and 1 case of deviation from the storage temperature for the investigational drug.

Table 1 List of Deviations from the Protocol

Subject Number	Reason for Deviation
KN-03-01	Head MRI examination within 2 weeks after a stroke-like attack not performed
KN-04-01	Deviation from MRI Imaging Conditions Confirmation Form
KN-05-01	Noncompliance for taking the investigational drugs
KN-08-01	Inspection specified for Week 0 not performed
KN-10-01	Deviation from storage temperature for investigational drug

4. Efficacy Evaluation

4.1. Analyzed Data Set

We decided on the handling of the data at the case study meeting held on January 21st, 2015. The breakdown of the group to be analyzed is shown in Table 4.1-1.

Of the total 10 cases registered, there were no subjects excluded from FAS and PPS. FAS and PPS were the same, with one subject with no L-arginine Co-administration and 9 cases with L-arginine Co-administration. Efficacy in this clinical trial was evaluated with the total cases. Further evaluation was performed with no L-arginine Co-Administration and L-arginine Co-Administration cases separately.

4.2. Characteristics of Demographics and Other Reference Values

Table 2.1 shows the characteristics of demographics and other reference values in the efficacy and safety analysis. Table 4.1-3 and Table 4.1-4 show the characteristics of demographics and other reference values in FAS and PPS.

There were 7 males and 3 females, and the average age was 29.1±11.49 years. The number of stroke-like attacks occurring 78 weeks before acquiring consent was 2 to 4, and use history of L-arginine intravenous preparation was present in 8 subjects. Mitochondrial DNA point mutations were observed in 9 subjects for A3243G and 1 subject for T3271C.

Table 2.1 Characteristics of demographic and other reference values

(Efficacy and Safety Analysis cases)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Gender: n (%)			
Male	7 (70.0)	1 (100.0)	6 (66.7)
Female	3 (30.0)	0 (0.0)	3 (33.3)
Age at consent acquisition (y)			
Number of cases	10	1	9
Mean	29.1	31.0	28.9
SD	11.49	-	12.17
Median, Minimum, Maximum	30.0, 14, 46	-, -, -	30.0, 14, 46
Age at consent acquisition (y) n (%)			
10-<20 y	3 (30.0)	0 (0.0)	3 (33.3)
20-<30 y	1 (10.0)	0 (0.0)	1 (11.1)
30-<40 y	4 (40.0)	1 (100.0)	3 (33.3)
40-<50 y	2 (20.0)	0 (0.0)	2 (22.2)
Number of stroke-like episodes[2)] within the 78 weeks[1)] period before consent: n (%)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)
2	4 (40.0)	0 (0.0)	4 (44.4)
3	2 (20.0)	1 (100.0)	1 (11.1)
4	4 (40.0)	0 (0.0)	4 (44.4)
The use of intravenous L-arginine administration within the 78 weeks[1)] period before consent: n (%)			
Yes	2 (20.0)	1 (100.0)	1 (11.1)
No	8 (80.0)	0 (0.0)	8 (88.9)

Table 2.2 Characteristics of demographic and other reference values

(Efficacy and Safety Analysis cases)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Point mutation of mitochondrial A3243G: n (%)			
No	1 (10.0)	1 (100.0)	0 (0.0)
Yes	9 (90.0)	0 (0.0)	9 (100.0)
Point mutation of mitochondrial T3271C: n (%)			
No	9 (90.0)	0 (0.0)	9 (100.0)
Yes	1 (10.0)	1 (100.0)	0 (0.0)
Point mutation of mitochondrial G3244A: n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Point mutation of mitochondrial T3258C: n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Point mutation of mitochondrial T3291C: n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Systolic BP (mmHg)			
N	10	1	9
Mean	119.7	124.0	119.2
SD	13.77	-	14.52
Median, Minimum, Maximum	119.5, 100, 147	-, -, -	115.0, 100, 147
Diastolic BP (mmHg)			
N	10	1	9
Mean	73.5	65.0	74.4
SD	12.94	-	13.35
Median, Minimum, Maximum	72.5, 52, 93	-, -, -	74.0, 52, 93
Pulse (beats/min)			
N	10	1	9
Mean	86.3	111.0	83.6
SD	15.68	-	13.86
Median, Minimum, Maximum	86.5, 64, 111	-, -, -	83.0, 64, 106
Height (cm)			
N	10	1	9
Mean	155.43	172.00	153.59
SD	10.208	-	8.894
Median, Minimum, Maximum	154.80, 140.3, 172.0	-, -, -	153.40, 140.3, 169.9
Body weight (kg)			
N	10	1	9
Mean	41.94	41.40	42.00
SD	8.346	-	8.850
Median, Minimum, Maximum	41.60, 32.0, 59.4	-, -, -	41.80, 32.0, 59.4

Table 2.3 Characteristics of demographic and other reference values

(Efficacy and Safety Analysis cases)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Body weight (kg)			
<15kg	0 (0.0)	0 (0.0)	0 (0.0)
15-<25kg	0 (0.0)	0 (0.0)	0 (0.0)
25-<40kg	4 (40.0)	0 (0.0)	4 (44.4)
40- kg	6 (60.0)	1 (100.0)	5 (55.6)
Complications: n (%)			
No	2 (20.0)	0 (0.0)	2 (22.2)
Yes	8 (80.0)	1 (100.0)	7 (77.8)
Smoking: n (%)			
No smoking episode	8 (80.0)	1 (100.0)	7 (77.8)
Current smoker	0 (0.0)	0 (0.0)	0 (0.0)
Previous smoker	2 (20.0)	0 (0.0)	2 (22.2)
Complications within the 78 weeks[1)] period before consent: n (%)			
No	8 (80.0)	1 (100.0)	7 (77.8)
Yes	2 (20.0)	0 (0.0)	2 (22.2)

Quoted from Table 4.1-5

1) Evaluation period of stroke-like episodes before starting the trial

2) High signal confirmation by MRI is not indispensable for the stroke-like- episodes, since the evaluation period of a stroke-like-episode is before the start of the trial.

4.3. Measurements of Treatment Compliance

For KN-04-01, it was confirmed by monitoring the investigational drug was taken according to the Protocol, except for the fact that there was 1 case of 5 g/dose overdose and 14 cases of 6 g/dose overdoses, which exceeded the specified amount of 4 g/dose administered within 4 weeks from the start of administration. At a case study meeting, it was judged that the overdoses in KN-04-01 did not affect the effectiveness and safety, and both FAS and PPS were included in the analysis target group.

4.4. Efficacy Results and Individual Subject Data

4.4.1. Analysis of Effectiveness

4.4.1.1. Primary Endpoint

1) 100% Responder Rate

The 100% responder rate for FAS is shown in Table 2.2. In addition, Table 4.2-3 to Table 4.2-6 show the results of examining by logistic regression the influence of background factors on the presence or absence of 100% responders.

The 100% responder rate for FAS was 60.0% (6/10 subjects, 95% confidence interval: 26.2 to 87.8) in all the cases, 100.0% (1/1 subject, 95% confidence interval: 2.5 to 100.0) with no L-arginine

Co-Administration, and 55.6% (5/9 subjects, 95% confidence interval: 21.2 to 86.3) with L-arginine Co-Administration.

The results for PPS are shown in Table 4.2-2.

Table 2.4 Primary endpoint of the efficacy: 100% responder rate (FAS)

	Total cases N = 10	No L-arginine Co-Administration cases N = 1	L-arginine Co-Administration cases N = 9
No stroke-like episodes during the evaluation period: n (%)	6 (60.0)	1 (100.0)	5 (55.6)
Clopper-Pearson (Exact 95% Confidential interval: CI)	26.2, 87.8	2.5, 100.0	21.2, 86.3

Quoted from Table 4.2-1

4.4.1.2. Secondary Endpoints

The results for PPS and FAS are shown in Table 4.2-13-32.

1) Presence or Absence of Improvement of Clinical Symptoms

Improvement of clinical symptoms using JMDRS for FAS is shown in Table 2.3.

The average value of the total JMDRS score for FAS was 15.2±6.68 at Week 0 to 17.0±9.20 at Week 52 (withdrawal), and no significant change was observed.

Table 2.5 Secondary endpoint of the efficacy (1) Presence or absence of clinical symptoms: JMDRS (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 1						
Speech: n (%)						
0	2 (20.0)	2 (20.0)	1 (100.0)	1 (100.0)	1 (11.1)	1 (11.1)
1	4 (40.0)	2 (20.0)	0 (0.0)	0 (0.0)	4 (44.4)	2 (22.2)
2	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
3	3 (30.0)	3 (30.0)	0 (0.0)	0 (0.0)	3 (33.3)	3 (33.3)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swallowing: n (%)						
0	9 (90.0)	10 (100.0)	1 (100.0)	1 (100.0)	8 (88.9)	9 (100.0)
1	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Handwriting: n (%)						
0	4 (40.0)	5 (50.0)	1 (100.0)	1 (100.0)	3 (33.3)	4 (44.4)
1	4 (40.0)	3 (30.0)	0 (0.0)	0 (0.0)	4 (44.4)	3 (33.3)
2	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
Cutting food-handling utensils: n (%)						
0	4 (40.0)	5 (50.0)	1 (100.0)	1 (100.0)	3 (33.3)	4 (44.4)
1	6 (60.0)	4 (40.0)	0 (0.0)	0 (0.0)	6 (66.7)	4 (44.4)
2	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 2.3 Secondary endpoint of the efficacy (1) Presence or absence of clinical symptoms: JMDRS (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 1: Activities of daily living						
Dressing: n (%)						
0	5 (50.0)	5 (50.0)	1 (100.0)	1 (100.0)	4 (44.4)	4 (44.4)
1	4 (40.0)	4 (40.0)	0 (0.0)	0 (0.0)	4 (44.4)	4 (44.4)
2	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hygiene: n (%)						
0	5 (50.0)	6 (60.0)	1 (100.0)	1 (100.0)	4 (44.4)	5 (55.6)
1	5 (50.0)	2 (20.0)	0 (0.0)	0 (0.0)	5 (55.6)	2 (22.2)
2	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Falling: n (%)						
0	10 (100.0)	9 (90.0)	1 (100.0)	1 (100.0)	9 (100.0)	8 (88.9)
1	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paroxysmal event (migraine, seizure): n (%)						
0	3 (30.0)	4 (40.0)	0 (0.0)	0 (0.0)	3 (33.3)	4 (44.4)
1	2 (20.0)	3 (30.0)	1 (100.0)	1 (100.0)	1 (11.1)	2 (22.2)
2	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
3	3 (30.0)	2 (20.0)	0 (0.0)	0 (0.0)	3 (33.3)	2 (22.2)
Total scores of Section 1						
Mean	5.6	5.6	1.0	1.0	6.1	6.1
SD	3.34	4.06	-	-	3.10	3.95
Median, Minimum, Maximum	5.5, 1, 11	6.0, 1, 12	-, -, -	-, -, -	6.0, 2, 11	7.0, 1, 12

Table 2.3 Secondary endpoint of the efficacy (1) Presence or absence of clinical symptoms: JMDRS (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 2: Motor						
Proximal muscle strength (modified MRC): n (%)						
0	8 (80.0)	7 (70.0)	1 (100.0)	1 (100.0)	7 (77.8)	6 (66.7)
1	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
2	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper limb coordination: n (%)						
0	4 (40.0)	7 (70.0)	1 (100.0)	1 (100.0)	3 (33.3)	6 (66.7)
1	5 (50.0)	2 (20.0)	0 (0.0)	0 (0.0)	5 (55.6)	2 (22.2)
2	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Walking: n (%)						
0	6 (60.0)	4 (40.0)	1 (100.0)	1 (100.0)	5 (55.6)	3 (33.3)
1	3 (30.0)	3 (30.0)	0 (0.0)	0 (0.0)	3 (33.3)	3 (33.3)
2	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Moderate motor activities: n (%)						
0	6 (60.0)	5 (50.0)	1 (100.0)	1 (100.0)	5 (55.6)	4 (44.4)
1	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
2	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
3	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Table 2.3 Secondary endpoint of the efficacy (1) Presence or absence of clinical symptoms: JMDRS (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Vigorous motor activities: n (%)						
0	1 (10.0)	2 (20.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (11.1)
1	2 (20.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (22.2)
2	4 (40.0)	1 (10.0)	0 (0.0)	0 (0.0)	4 (44.4)	1 (11.1)
3	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
4	2 (20.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (22.2)
Total scores of Section 2						
Mean	4.4	4.8	0.0	0.0	4.9	5.3
SD	3.72	4.08	-	-	3.59	3.94
Median, Minimum, Maximum	3.5, 0, 13	4.5, 0, 13	-, -, -	-, -, -	4.0, 1, 13	5.0, 0, 13

Table 2.3 Secondary endpoint of the efficacy (1) Presence or absence of clinical symptoms: JMDRS (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 3: Special sensory						
Vision: n (%)						
0	8 (80.0)	7 (70.0)	1 (100.0)	1 (100.0)	7 (77.8)	6 (66.7)
1	2 (20.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (22.2)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Auditory: n (%)						
0	1 (10.0)	2 (20.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (11.1)
1	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)
2	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
3	5 (50.0)	4 (40.0)	0 (0.0)	0 (0.0)	5 (55.6)	4 (44.4)
4	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
Total scores of Section 3						
Mean	2.5	2.9	0.0	0.0	2.8	3.2
SD	1.35	1.85	-	-	1.09	1.64
Median, Minimum, Maximum	3.0, 0, 4	3.0, 0, 7	-, -, -	-, -, -	3.0, 1, 4	3.0, 1, 7

Table 2.3 Secondary endpoint of the efficacy (1) Presence or absence of clinical symptoms: JMDRS (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 4:						
Endocrine: n (%)						
0	7 (70.0)	7 (70.0)	1 (100.0)	1 (100.0)	6 (66.7)	6 (66.7)
1	3 (30.0)	2 (20.0)	0 (0.0)	0 (0.0)	3 (33.3)	2 (22.2)
2	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 4						
Mean	0.3	0.4	0.0	0.0	0.3	0.4
SD	0.48	0.70	-	-	0.50	0.73
Median, Minimum, Maximum	0.0, 0, 1	0.0, 0, 2	-, -, -	-, -, -	0.0, 0, 1	0.0, 0, 2

Table 2.3 Secondary endpoint of the efficacy (1) Presence or absence of clinical symptoms: JMDRS (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 5						
Cardiac complications: n (%)						
0	5 (50.0)	4 (40.0)	1 (100.0)	1 (100.0)	4 (44.4)	3 (33.3)
1	5 (50.0)	6 (60.0)	0 (0.0)	0 (0.0)	5 (55.6)	6 (66.7)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 5						
Mean	0.5	0.6	0.0	0.0	0.6	0.7
SD	0.53	0.52	-	-	0.53	0.50
Median, Minimum, Maximum	0.5, 0, 1	1.0, 0, 1	-, -, -	-, -, -	1.0, 0, 1	1.0, 0, 1

Table 2.3 Secondary endpoint of the efficacy (1) Presence or absence of clinical symptoms: JMDRS (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 6 Renal function: n (%)						
0	9 (90.0)	9 (90.0)	0 (0.0)	1 (100.0)	9 (100.0)	8 (88.9)
Section 6						
Renal function: n (%)						
0	9 (90.0)	9 (90.0)	0 (0.0)	1 (100.0)	9 (100.0)	8 (88.9)
1	1 (10.0)	1 (10.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total score of Section 6						
Mean	0.1	0.1	1.0	0.0	0.0	0.1
SD	0.32	0.32	-	-	0.00	0.33
Median, Minimum, Maximum	0.0, 0, 1	0.0, 0, 1	-, -, -	-, -, -	0.0, 0, 0	0.0, 0, 1

Table 2.3 Secondary endpoint of the efficacy (1) Presence or absence of clinical symptoms: JMDRS (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 7: Cognitive impairment						
Intellectual impairment: n (%)						
0	2 (20.0)	2 (20.0)	1 (100.0)	1 (100.0)	1 (11.1)	1 (11.1)
1	7 (70.0)	4 (40.0)	0 (0.0)	0 (0.0)	7 (77.8)	4 (44.4)
2	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)
3	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Motivation and drive: n (%)						
0	5 (50.0)	3 (30.0)	1 (100.0)	1 (100.0)	4 (44.4)	2 (22.2)
1	3 (30.0)	3 (30.0)	0 (0.0)	0 (0.0)	3 (33.3)	3 (33.3)
2	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
3	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 7						
Mean	1.8	2.6	0.0	0.0	2.0	2.9
SD	1.62	2.01	-	-	1.58	1.90
Median, Minimum, Maximum	1.5, 0, 5	2.5, 0, 6	-, -, -	-, -, -	2.0, 0, 5	3.0, 0, 6
Total score of Section 1-7						
Mean	15.2	17.0	2.0	1.0	16.7	18.8
SD	6.68	9.20	-	-	5.10	7.73
Median, Minimum, Maximum	15.0, 2, 28	18.0, 1, 32	-, -, -	-, -, -	16.0, 11, 28	20.0, 9, 32

Quoted from Table 4.2-13

2) 50% Responder Rate

Table 2.4 shows the 50% responder rate for FAS. Table 4.2-7 to Table 4.2-10 show the influence of background factors on the presence or absence of 50% responders (logistic regression).

The 50% responder rate for FAS was 80.0% (8/10 subjects, 95% confidence interval: 44.4 to 97.5) in all cases, 100.0% (1/1 subject, 95% confidence interval: 2.5 To 100.0) with no L-arginine Co-Administration, and 77.8% (7/9 subjects, 95% confidence interval: 40.0 to 97.2) with L-arginine Co-Administration.

The results for PPS are shown in Table 4.2-16.

Table 2.6 Secondary endpoint of the efficacy (2)

50% responder rate (FAS)

	Total cases N = 10	No L-arginine Co-Administration cases N = 1	L-arginine Co-Administration cases N = 9
The percentage of cases with 50% or more reduction in stroke-like episodes during the trial period, in comparison with the number of stroke-like episodes during the pretrial period			
n (%)	8 (80.0)	1 (100.0)	7 (77.8)
Clopper-Pearson (Exact 95% Confidential interval: CI)	44.4, 97.5	2.5, 100.0	40.0, 97.2

Quoted from Table 4.2-15

3) Number of Occurrences of abrupt-onset focal neurological deficits (one of the stroke-like episodes criteria for this study), irrespective of high signal confirmation in head MRI diffusion weighted images

Table 2.5 shows the number of occurrences of episodic local nerve signs during attacks (one of the stroke criteria for MELAS strokes) in FAS.

The frequency of occurrences of abrupt-onset focal neurological deficits for FAS was more than 2 times in all the cases 78 weeks before acquisition of consent; but after investigational drug administration, the occurrence of abrupt-onset focal neurological deficits was not observed in 4 subjects, and was observed 1 time in the remaining 6 subjects.

The results for PPS are shown in Table 4.2-18.

Table 2.7 Secondary endpoint of the efficacy (3)

Number of abrupt onset focal neurological deficits defined by the MELAS stroke diagnostic criteria with no consideration of confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period N = 10	Trial period N = 10	Pretrial period N = 1	Trial period N = 1	Pretrial period N = 9	Trial period N = 9
Episodes: n (%)						
0	0 (0.0)	4 (40.0)	0 (0.0)	1 (100.0)	0 (0.0)	3 (33.3)
1	0 (0.0)	6 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
2	4 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (44.4)	0 (0.0)
3	2 (20.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (11.1)	0 (0.0)
4	4 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (44.4)	0 (0.0)
Frequency of episodes per month[1)]						
Mean	0.170	0.055	0.154	0.000	0.172	0.061
SD	0.0561	0.0475	-	-	0.0591	0.0460
Median, Minimum, Maximum	0.164, 0.10, 0.28	0.090, 0.00, 0.10	-, -, -	-, -, -	0.173, 0.10, 0.28	0.090, 0.00, 0.10

Quoted from 3.2-17

4) Special Examinations (lactic acid value, pyruvic acid value, lactic acid to pyruvic acid ratio, and taurine value in the blood and in the CSF)

For FAS, the changes in measured values at the time of each evaluation in the special examinations from Week 0 to Week 52 (withdrawal) are shown in Table 2.6.

For FAS, there was no marked change in blood and spinal fluid lactic acid value, pyruvic acid value, or lactic acid to pyruvic acid ratio at Week 0 and Week 52 (or when canceled) of investigational drug administration.

The results for PPS are shown in Table 4.2-20.

Table 2.8 Secondary endpoint of the efficacy (4)

Special examination (FAS)

	Total cases			No L-arginine Co-Administration cases			L-arginine Co-Administration cases		
	0 wks N=10	52 wks (or when canceled) N=10	From 0 wks rate of change N=10	0 wks N=1	52 wks (or when canceled) N=1	From 0 wks rate of change N=1	0 wks N=9	52 wks (or when canceled) N=9	From 0 wks rate of change N=9
Lactic acid in blood (mg/dL)									
n	10	10	10	1	1	1	9	9	9
Mean	32.5	35.8	13.60	25.2	23.8	-5.56	33.3	37.1	15.73
SD	12.97	12.64	30.857	-	-	-	13.48	12.64	31.941
Median	27.0	35.1	8.73	-	-	-	27.5	40.1	9.09
Minimum, Maximum	18, 64	17, 55	-35.1, 70.8	-, -	-, -	-, -	18, 64	17, 55	-35.1, 70.8
Lactic acid in CSF (mg/dL)									
n	7	7	7	1	1	1	6	6	6
Mean	40.5	45.7	22.56	23.6	17.0	-27.97	43.4	50.5	30.98
SD	15.31	17.87	66.000	-	-	-	14.64	13.81	68.055
Median	46.2	46.5	-3.94	-	-	-	49.1	50.1	6.23
Minimum, Maximum	24, 56	17, 67	-28.0, 159.1	-, -	-, -	-, -	24, 56	34, 67	-25.5, 159.1
Pyruvic acid in blood (mg/dL)									
n	10	10	10	1	1	1	9	9	9
Mean	1.3	1.4	19.15	1.5	1.3	-14.97	1.2	1.4	22.94
SD	0.39	0.51	48.942	-	-	-	0.41	0.53	50.330
Median	1.2	1.2	5.81	-	-	-	1.2	1.2	11.63
Minimum, Maximum	1, 2	1, 2	-37.4, 124.2	-, -	-, -	-, -	1, 2	1, 2	-37.4, 124.2
Pyruvic acid in CSF (mg/dL)									
n	7	7	7	1	1	1	6	6	6
Mean	1.4	1.7	29.78	1.0	0.8	-18.81	1.5	1.9	37.88
SD	0.39	0.52	55.475	-	-	-	0.38	0.37	56.053
Median	1.4	1.7	11.63	-	-	-	1.6	1.8	14.42
Minimum, Maximum	1, 2	1, 2	-18.8, 142.4	-, -	-, -	-, -	1, 2	1, 2	-5.2, 142.4

Table 2.6 Secondary endpoint of the efficacy (4)

Special examination (FAS)

	Total cases			No L-arginine Co-Administration cases			L-arginine Co-Administration cases		
	0 wks N=10	52 wks (or when canceled) N=10	From 0 wks rate of change N=10	0 wks N=1	0 wks N=1	52 wks (or when canceled) N=1	From 0 wks rate of change N=9	52 wks (or when canceled) N=9	0 wks N=9
Ratio of lactic acid / pyruvic acid in blood									
n	10	10	10	1	1	1	9	9	9
Mean	26.14	25.51	0.80	17.14	19.04	11.07	27.14	26.23	-0.34
SD	5.915	4.891	22.899	-	-	-	5.303	4.592	23.985
Median	27.87	24.73	-1.40	-	-	-	29.41	24.93	-2.27
Minimum, Maximum	16.3, 32.0	19.0, 34.0	-23.8, 47.1	-, -	-, -	-, -	16.3, 32.0	19.8, 34.0	-23.8, 47.1
Ratio of lactic acid / pyruvic acid in CSF									
n	7	7	7	1	1	1	6	6	6
Mean	28.47	26.03	-8.31	23.37	20.73	-11.28	29.32	26.92	-7.82
SD	4.934	4.678	9.324	-	-	-	4.810	4.438	10.114
Median	26.55	27.75	-11.28	-	-	-	28.36	27.83	-8.85
Minimum, Maximum	23.4, 36.9	20.7, 32.5	-21.5, 6.9	-, -	-, -	-, -	23.9, 36.9	20.8, 32.5	-21.5, 6.9
Blood taurine concentration (nmol/mL)									
n	10	10	10	1	1	1	9	9	9
Mean	57.6	945.7	1786.12	57.4	1168.5	1935.71	57.6	920.9	1769.50
SD	20.29	406.18	1288.851	-	-	-	21.53	422.73	1365.895
Median	57.7	1071.8	1376.78	-	-	-	57.9	1028.1	1216.46
Minimum, Maximum	29, 102	189, 1579	226.3, 4359.6	-, -	-, -	-, -	29, 102	189, 1579	226.3, 4359.6
CSF taurine concentration (nmol/mL)									
n	7	7	7	1	1	1	6	6	6
Mean	11.2	42.1	283.26	9.1	30.5	235.16	11.6	44.1	291.27
SD	2.88	13.77	134.531	-	-	-	2.99	14.01	145.529
Median	9.8	39.6	235.44	-	-	-	11.1	42.9	242.21
Minimum, Maximum	8, 16	27, 66	191.8, 583.5	-, -	-, -	-, -	8, 16	27, 66	191.8, 583.5

Quoted from 3.2-19

5) Image Examinations (Head MRI Examinations)

The diffusion weighted images (axial) of the head MRI examinations for FAS and the results of other head MRI examinations are shown in Table 2.7 and Table 2.8.

For FAS, subjects with new abnormal findings after Week 52 (or when canceled) of investigational drug administration included: 2 cases of diffusion weighted images (axial), 3 cases of T1 weighted images (axial), 1 ADC map (axial); the 2 cases of diffusion weighted images (axial) and T1 weighted images (axial) were in the same subject. No marked deterioration was observed after investigational drug administration.

The results for PPS are shown in Table 4.2-22 and Table 4.2-24.

Table 2.7 Secondary endpoint of the efficacy (5)

Shift of the diffusion-weighted images (axial) on the brain MRI (FAS)

		52 wks (or when canceled)				
	-1 wks	Normal	Abnormal (Hyperintense lesion)	Abnormal (others)	Not examined	Total
Diffusion-weighted images (axial)						
Total cases (N=10)						
Normal	8 (80.0)	6 (100.0)	2 (50.0)	0 (0.0)	0 (0.0)	8 (80.0)
Abnormal (Hyperintense lesion)	2 (20.0)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	2 (20.0)
Abnormal (Others)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	6 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration cases (N=1)						
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal (Hyperintense lesion)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal (Others)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)						
Normal	7 (77.8)	5 (100.0)	2 (50.0)	0 (0.0)	0 (0.0)	7 (77.8)
Abnormal (Hyperintense lesion)	2 (22.2)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	2 (22.2)
Abnormal (Others)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	5 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	9 (100.0)

Quoted from Table 4.2-21

Table 2.8 Secondary endpoint of the efficacy (5)

Shift other than the diffusion-weighted images on the brain MRI (FAS)

		52 wks (or when canceled)			
	-1 wks	Normal	Abnormal	Not examined	Total
MRA (intracranial)					
Total (N=10)					
Normal	10 (100.0)	10 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	10 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	9 (100.0)	9 (100.0)	0 (0.0)	0 (0.0)	9 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	9 (100.0)	0 (0.0)	0 (0.0)	9 (100.0)
FLAIR methods (axial)					
Total (N=10)					
Normal	2 (20.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (20.0)
Abnormal	8 (80.0)	0 (0.0)	8 (100.0)	0 (0.0)	8 (80.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	2 (100.0)	8 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	1 (11.1)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)
Abnormal	8 (88.9)	0 (0.0)	8 (100.0)	0 (0.0)	8 (88.9)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	1 (100.0)	8 (100.0)	0 (0.0)	9 (100.0)

Table 2.8 Secondary endpoint of the efficacy (5)

Shift other than the diffusion-weighted images on the brain MRI (FAS)

		52 wks (or when canceled)			
	-1 wks	Normal	Abnormal	Not examined	Total
T2-weighted images (axial)					
Total (N=10)					
Normal	2 (20.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (20.0)
Abnormal	8 (80.0)	0 (0.0)	8 (100.0)	0 (0.0)	8 (80.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	2 (100.0)	8 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	1 (11.1)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)
Abnormal	8 (88.9)	0 (0.0)	8 (100.0)	0 (0.0)	8 (88.9)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	1 (100.0)	8 (100.0)	0 (0.0)	9 (100.0)
T1-weighted images (axial)					
Total (N=10)					
Normal	5 (50.0)	2 (100.0)	3 (37.5)	0 (0.0)	5 (50.0)
Abnormal	5 (50.0)	0 (0.0)	5 (62.5)	0 (0.0)	5 (50.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	2 (100.0)	8 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	4 (44.4)	1 (100.0)	3 (37.5)	0 (0.0)	4 (44.4)
Abnormal	5 (55.6)	0 (0.0)	5 (62.5)	0 (0.0)	5 (55.6)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	1 (100.0)	8 (100.0)	0 (0.0)	9 (100.0)

Table 2.8 Secondary endpoint of the efficacy (5)

Shift other than the diffusion-weighted images on the brain MRI (FAS)

		52 wks (or when canceled)			
	-1 wks	Normal	Abnormal	Not examined	Total
T2*-weighted images (axial)					
Total (N=10)					
Normal	8 (80.0)	8 (100.0)	0 (0.0)	0 (0.0)	8 (80.0)
Abnormal	2 (20.0)	0 (0.0)	2 (100.0)	0 (0.0)	2 (20.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	8 (100.0)	2 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	7 (77.8)	7 (100.0)	0 (0.0)	0 (0.0)	7 (77.8)
Abnormal	2 (22.2)	0 (0.0)	2 (100.0)	0 (0.0)	2 (22.2)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	7 (100.0)	2 (100.0)	0 (0.0)	9 (100.0)
ADC map (axial)					
Total (N=10)					
Normal	7 (70.0)	6 (85.7)	1 (33.3)	0 (0.0)	7 (70.0)
Abnormal	3 (30.0)	1 (14.3)	2 (66.7)	0 (0.0)	3 (30.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	7 (100.0)	3 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	6 (66.7)	5 (83.3)	1 (33.3)	0 (0.0)	6 (66.7)
Abnormal	3 (33.3)	1 (16.7)	2 (66.7)	0 (0.0)	3 (33.3)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	6 (100.0)	3 (100.0)	0 (0.0)	9 (100.0)

Quoted from Table 4.2-23

6) Number of Times L-arginine Intravenous Preparation was Used Before and After Administration of Investigational Drug

For FAS, the number of times the L-arginine intravenous preparation was used before and after investigational drug administration (not considering MRI confirmation) and the number of times the L-arginine intravenous preparation was administered before and after investigational drug administration (considering MRI confirmation) are shown in Table 2.9 and Table 2.10.

When MRI confirmation was not taken into consideration, for FAS, the number of uses of the L-arginine intravenous preparation per one abrupt-onset focal neurological deficits (total 30

episodes) before investigational drug administration was 14 (1 case), 13 (1 case), 12 (1 case), 9 (1 case), 8 (3 cases), 7 (1 case), 4 (1 case), 2 (4 cases), 1 (5 cases), and 0 (12 cases); the number was (of the 6 attacks total): 7 (1 case), 2 (1 case), 1 (1 case), and 0 (3 cases) after investigational drug administration, A similar tendency was also observed when MRI confirmation was taken into consideration.

The results for PPS are shown in Table 4.2-26 and Table 4.2-28.

Table 2.9 Secondary endpoint of the efficacy (6)

Frequency of intravenous formulation with L-arginine during pretrial and trial periods

: Stroke-like episodes, not confirmed by abnormal signal intensity on MRI (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
Number of administration: n (%)						
Number of cases	10	10	1	1	9	9
0 times	2 (20.0)	7 (70.0)	1 (100.0)	1 (100.0)	1 (11.1)	6 (66.7)
1 times	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
2 times	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
5 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
6 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
7 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
8 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
36 times	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)

Table 2.9 Secondary endpoint of the efficacy (6)

Frequency of intravenous formulation with L-arginine during pretrial and trial periods

: Stroke-like episodes, not confirmed by abnormal signal intensity on MRI (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
Number of the administration frequencies of intravenous L-arginine per one stroke-like episode: n (%)						
Total stroke-like episodes	30	6	3	0	27	6
0 time	12 (40.0)	3 (50.0)	3 (100.0)	0 (0.0)	9 (33.3)	3 (50.0)
1 time	5 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	5 (18.5)	1 (16.7)
2 times	4 (13.3)	1 (16.7)	0 (0.0)	0 (0.0)	4 (14.8)	1 (16.7)
3 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
5 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
7 times	1 (3.3)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.7)	1 (16.7)
8 times	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.1)	0 (0.0)
9 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
10 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
11 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
12 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
13 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
14 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)

Quoted from Table 4.2-25

1) "Before administration" is the evaluation period of the stroke-like episodes before the start of the trial, "after administration" is the evaluation period of the stroke-like episodes after the start of the trial

2) Total number of times L-arginine intravenous preparation was used for "abrupt-onset of focal neurological deficits" with or without high signal confirmation by MRI

3) The expression within 2 weeks is counted as "one time" for " abrupt-onset of focal neurological deficits" with or without confirmation of high signal by MRI

4) Total number of uses of L-arginine intravenous preparation for one stroke-like episode

Table 2.10 Secondary endpoint of the efficacy (6)

Frequency of intravenous formulation with L-arginine during pretrial and trial periods

: Stroke-like episodes, confirmed by abnormal signal intensity on MRI (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Pretrial period	Trial period	Pretrial period
Number of administration: n (%)						
Number of cases	10	10	1	1	9	9
0 times	5 (50.0)	7 (70.0)	1 (100.0)	1 (100.0)	4 (44.4)	6 (66.7)
1 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
2 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
4 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
5 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
7 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
8 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
35 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
36 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)

Table 2.10 Secondary endpoint of the efficacy (6)

Frequency of intravenous formulation with L-arginine during pretrial and trial periods

: Stroke-like episodes, confirmed by abnormal signal intensity on MRI (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Pretrial period	Trial period	Pretrial period
Number of the administration frequencies of intravenous L-arginine per one stroke-like episode: n (%)						
Total stroke-like episodes	17	4	2	0	15	4
0 times	5 (29.4)	1 (25.0)	2 (100.0)	0 (0.0)	3 (20.0)	1 (25.0)
1 times	1 (5.9)	1 (25.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (25.0)
2 times	2 (11.8)	1 (25.0)	0 (0.0)	0 (0.0)	2 (13.3)	1 (25.0)
3 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
5 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
7 times	1 (5.9)	1 (25.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (25.0)
8 times	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (20.0)	0 (0.0)
9 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
10 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
11 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
12 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
13 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
14 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)

Quoted from Table 4.2-27

1) "Before administration" is the evaluation period of the stroke-like episodes before the start of the trial, "after administration" is the evaluation period of the stroke-like episodes after the start of the trial.

2) Total number of times L-arginine intravenous preparation was used for "abrupt-onset of focal neurological deficits" with or without high signal confirmation by MRI.

3) The expression within 2 weeks was counted as "one time" for "abrupt-onset of focal neurological deficits" with or without confirmation of high signal by MRI.

4) Total number of uses of L-arginine intravenous preparation for one stroke-like episode.

7) Number of High Signal Confirmations When Head MRI was Performed upon Occurrence of Headache, Nausea and Vomiting, Convulsions, and Disturbed Consciousness

Table 2.11 shows the number of high signal confirmations when head MRIs were performed upon occurrence of headache, nausea and vomiting, convulsions, and disturbed consciousness for FAS.

For FAS, symptoms other than abrupt-onset focal neurological deficits after investigational drug administration were observed twice in 2 subjects, among which high signal was disclosed only once in 1 subject.

The results for PPS are shown in Table 4.2-30.

Table 2.11 Secondary endpoint of the efficacy (7)

Number of times high-intensity lesion(s) are confirmed with diffusion-weighted brain MRI in the presence of headache, nausea/vomiting, convulsions, or impaired consciousness (FAS)

	Total cases N = 10	No L-arginine Co-Administration cases N = 1	L-arginine Co-Administration cases N = 9
n (%)			
0 times	9 (90.0)	1 (100.0)	8 (88.9)
1 times	1 (10.0)	0 (0.0)	1 (11.1)

Quoted from Table 4.2-29

4.4.1.3. Other Endpoints

1) MMSE

Measurement values and summary statistics of MMSE scores for FAS are shown in Table 2.12. For FAS, the MMSE score was 24.2±3.74 at Week 0 and 25.1±4.37 at Week 52 of administration. No significant change was observed after investigational drug administration.

The results for PPS are shown in Table 4.2-32.

Table 2.12 MMSE score (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N=10	52wks(or when cancelled) N=9	0 wks N=1	52wks(or when cancelled) N=1	0 wks N=9	52wks(or when cancelled) N=8
Orientation to time: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
4	1 (10.0)	3 (33.3)	0 (0.0)	0 (0.0)	1 (11.1)	3 (37.5)
5	8 (80.0)	6 (66.7)	1 (100.0)	1 (100.0)	7 (77.8)	5 (62.5)

Table 2.12 MMSE score (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N=10	52wks(or when cancelled) N=9	0 wks N=1	52wks(or when cancelled) N=1	0 wks N=9	52wks(or when cancelled) N=8
Orientation to place: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
2	1 (10.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)	1 (12.5)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	4 (40.0)	1 (11.1)	0 (0.0)	0 (0.0)	4 (44.4)	1 (12.5)
5	5 (50.0)	6 (66.7)	1 (100.0)	1 (100.0)	4 (44.4)	5 (62.5)
Registration: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)
3	8 (80.0)	9 (100.0)	1 (100.0)	1 (100.0)	7 (77.8)	8 (100.0)
Attention and calculation: n (%)						
0	2 (20.0)	2 (22.2)	0 (0.0)	0 (0.0)	2 (22.2)	2 (25.0)
1	4 (40.0)	1 (11.1)	1 (100.0)	0 (0.0)	3 (33.3)	1 (12.5)
2	2 (20.0)	3 (33.3)	0 (0.0)	0 (0.0)	2 (22.2)	3 (37.5)
3	1 (10.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)	1 (12.5)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	1 (10.0)	2 (22.2)	0 (0.0)	1 (100.0)	1 (11.1)	1 (12.5)
Recall: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	2 (20.0)	1 (11.1)	1 (100.0)	0 (0.0)	1 (11.1)	1 (12.5)
3	8 (80.0)	8 (88.9)	0 (0.0)	1 (100.0)	8 (88.9)	7 (87.5)
Naming: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	10 (100.0)	9 (100.0)	1 (100.0)	1 (100.0)	9 (100.0)	8 (100.0)
Repetition: n (%)						
0	5 (50.0)	3 (33.3)	0 (0.0)	0 (0.0)	5 (55.6)	3 (37.5)
1	5 (50.0)	6 (66.7)	1 (100.0)	1 (100.0)	4 (44.4)	5 (62.5)
Talking instructions: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
3	9 (90.0)	9 (100.0)	1 (100.0)	1 (100.0)	8 (88.9)	8 (100.0)
Write instructions: n (%)						
0	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
1	10 (100.0)	8 (88.9)	1 (100.0)	1 (100.0)	9 (100.0)	7 (87.5)

Table 2.12 MMSE score (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N=10	52wks(or when cancelled) N=9	0 wks N=1	52wks(or when cancelled) N=9	0 wks N=10	52wks(or when cancelled) N=9
Spontaneous writing: n (%)						
0	1 (10.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)	1 (12.5)
1	9 (90.0)	8 (88.9)	1 (100.0)	1 (100.0)	8 (88.9)	7 (87.5)
Figure reproduction: n (%)						
0	3 (30.0)	2 (22.2)	0 (0.0)	0 (0.0)	3 (33.3)	2 (25.0)
1	7 (70.0)	7 (77.8)	1 (100.0)	1 (100.0)	6 (66.7)	6 (75.0)
Total score						
Number of cases	10	9	1	1	9	8
Mean	24.2	25.1	25.0	30.0	24.1	24.5
SD	3.74	4.37	-	-	3.95	4.24
Media, Minimum, Maximum	25.0, 16, 30	27.0, 19, 30	-, -, -	-, -, -	25.0, 16, 30	26.0, 19, 30

Quoted from Table 4.2-31

2) Mitochondrial Gene Mutation Rate, Taurine Modification Rare in the mitochondrial $tRNA^{Leu(UUR)}$, and ND6 Protein Mass in the peripheral blood leukocytes

Table 4.3.4-7 shows leukocyte mitochondrial gene mutation rate, taurine modification rate in the mitochondrial $tRNA^{Leu(UUR)}$, and ND6 protein mass.

The rate of taurine modification in the mitochondrial $tRNA^{Leu(UUR)}$ increased from Week 0 to Week 52 (or when canceled), in 5 out of 9 cases. There was no significant change in mitochondrial gene mutation rate or ND6 protein mass.

4.4.2. Statistical and Analytical Points

4.4.2.1. Covariate Adjustment

Covariate adjustment was not performed in this trial.

4.4.2.2. Handling of Dropouts and Missing Values

Final handling of missing values, outliers, and analytical periods was decided before fixing the data in a permanent form by referring to the opinions and advice from medical experts as necessary. Subjects or data points excluded from analysis are posted in the summary table for the individual tables, but are excluded from tallies such as summary statistics.

4.4.2.3. Intermediate Analysis and Data Monitoring

Intermediate analysis and data monitoring were not carried out in this trial.

4.4.2.4. Multicenter Trial

This trial was conducted at 10 institutions, and a total of 10 subject data sets were collected. Because there were a small number of subjects per facility, we did not compile endpoints with respect to facility.

4.4.2.5. Multiple Comparison and Multiplicity

Multiple comparison and multiplicity were not carried out in this trial.

4.4.2.6. Use of "Efficacy Evaluation" for Cases

The main analysis cases (total cases, no L-arginine Co-Administration cases, and L-arginine Co-Administration cases) for effectiveness were FAS, but in order to show the robustness of the analysis results for FAS, analysis of PPS was also conducted. In this trial, FAS and PPS were consistent.

4.4.2.7. Tests Using Actual Control Drugs Intended to Demonstrate Equivalence

Tests using actual control drugs intended to demonstrate equivalence were not carried out in this trial.

4.4.2.8. Investigation of Total Cases, no L-arginine Co-Administration Cases, and L-arginine Co-Administration Cases

1) Total cases, cases with and without L-arginine Co-Administration was conducted.

The definitions used are as follows.

- Cases with L-arginine Co-Administration: Cases who did not use L-arginine, and who had 2 or more stroke-like attacks in the 78 weeks before consent was obtained, and who had at least 1 stroke-like attack in the 52 weeks before consent was obtained.
- Cases with no Co-Administration: Cases who used L-arginine for at most 78 weeks, and who had 2 or more stroke-like attacks in that period, and who had at least 1 stroke-like attack in the 52 weeks before consent was obtained. Alternatively, subjects who used L-arginine for more than 78 weeks, and who had 2 or more stroke-like attacks in that period, and who had at least 1 stroke-like attack in the 52 weeks before consent was obtained.

2) At the 100% responder rate and 50% responder rate, the following cases were examined.

- Cases in whom at least 2 stroke-like attacks (those satisfying the MELAS stroke criteria) were observed in the 78 weeks before consent were obtained.
- Cases in whom at least 2 abrupt-onset focal neurological deficits (regardless of head MRI confirmation of high signal) were observed in the 78 weeks before consent was obtained, and in

whom at least 1 local nerve sign (regardless of head MRI confirmation of high signal) was observed.

- Cases in whom at least 2 local nerve signs (regardless of head MRI confirmation of high signal) were observed in the 78 weeks before consent was obtained.
- Cases in whom at least 2 stroke-like attacks (those satisfying the MELAS stroke criteria) were observed in the 52 weeks before consent were obtained.
- Cases in whom at least 2 abrupt-onset focal neurological deficits (regardless of confirmation of high signal by head MRI) were observed in the 52 weeks before consent was obtained.

These results are shown in Table 4.2-11 and Table 4.2-12.

4.4.3. Tabulation of Individual Reaction Data

List of presence/absence (JMDRS) of improvement in clinical symptoms for each subject, list of special examinations, list of image examinations (head MRI examination), list of L-arginine intravenous preparation usage before and after investigational drug administration, MMSE score list, and list of attacks and other symptoms are tabulated, respectively.

4.4.4. Drug Dose, Drug Concentration, and Their Relationship to Reactions

The administration details and the administration details for each subject are shown are tabulated.

4.4.5. Drug-drug and Drug-subject Interactions

Drug-drug and drug-subject interactions were not investigated in this trial.

4.4.6. Display for Each Subject

A list of efficacy data for each subject is tabulated.

4.4.7. Conclusion of Effectiveness

- The 100% responder rate was 60.0% (6/10 subjects, 95% confidence interval: 26.2 to 87.8) in all the cases, 100.0% (1/1 subject, 95% confidence interval: 2.5 to 100.0) with no L-arginine Co-Administration cases, and 55.6% (5/9 subjects, 95% confidence interval: 21.2 to 86.3) with L-arginine Co-Administration cases.
- The average total JMDRS score increased from 15.2±6.7 at Week 0 to 17.0±9.2 at Week 52 (withdrawal).
- The 50% responder rate was 80.0% (8/10 subjects, 95% confidence interval: 44.4 to 97.5) in all the cases, 100.0% (1/1 subject, 95% confidence interval: 2.5 to 100.0) with no L-arginine Co-Administration cases, and 77.8% (7/9 subjects, 95% confidence interval: 40.0 to 97.2) with L-arginine Co-Administration cases.

- The number of abrupt-onset focal neurological deficits defined in the MELAS stroke diagnostic criteria was more than 2 in total cases before administration of the investigational drug. Abrupt-onset focal neurological deficits were completely prevented in 4 subjects after the administration of the investigational drug. One episode was observed in the remaining 6 cases, respectively.
- At Week 0 and Week 52 (or when canceled) of investigational drug administration, there was no marked change in lactic acid value, pyruvic acid value, and lactic acid to pyruvic acid ratio in the blood and spinal fluid.
- After Week 52 (or when canceled) of investigational drug administration, new abnormalities were confirmed in head MRI laboratory findings 6 times in 4 subjects [2 cases of diffusion weighted images (axial), 3 cases of T1 weighted images (axial), and 1 case of ADC map (axial)]. Among them, 2 cases of diffusion weighted images (axial) and 2 cases of T1 weighted images (axial) were in the same case.
- Each investigator judged the use of L-arginine intravenous preparation when abrupt-onset focal neurological deficits occurs without confirmation of the MRI abnormality. Before investigational drug administration, the number of uses of L-arginine intravenous preparation per one episode (total 30 episodes) was 14 (1 case), 13 (1 case), 12 (1 case), 9 (1 case), 8 (3 cases), 7 (1 case), 4 (1 case), 2 (4 cases), 1 (5 cases), 0 (12 cases); after administration, of the number of uses per episodes (total 6 episodes) was 7 (1 case), 2 (1 case), 1 (1 case), and 0 (3 cases). Similar results were observed with confirmation of the MRI abnormality.
- Symptoms other than abrupt-onset focal neurological deficits were observed after investigational drug administration twice in 2 cases, among which a high signal was confirmed once in 1 case.
- The rate of the taurine modification in the mitochondrial $tRNA^{Leu(UUR)}$ in peripheral blood leukocytes significantly increased from Week 0 to Week 52 (or when canceled) in 5 out of 9 subjects.

Noteworthy, six out of total 10 cases achieved complete disappearance of stroke-like attacks, which was the primary endpoint. The lower limit of the 95% confidence interval was 26.2% for all cases and 21.1% for L-arginine Co-Administration cases, which was significantly higher than the threshold responder rate set in the protocol. The 50% responder rate also showed a high value of 80%. A significant decrease in the frequency of occurrence of abrupt-onset focal neurological deficits and the number of times usages of L-arginine intravenous preparation, and a significant increase in the taurine modification rate in the mitochondrial $tRNA^{Leu(UUR)}$ in the peripheral blood leukocytes were observed at Week 52 (or when canceled) of investigational drug administration. These results demonstrated the effectiveness of the investigational drug.

5. Safety Evaluation

5.1. Number of Cases Administered the Investigational Drug, Duration, and Dose

In this clinical trial, all the cases that were enrolled and administered the investigational drug were assigned to analyze the safety. All the 10 cases registered were administrated the investigational drug and included in the safety analysis.

The list of administration details and the administration details for each case are tabulated, respectively. The average number of days in which the drug was taken was 363.1±6.69, and the medication rate was 99.42±9.877%. Four cases had a dose of 9 g/day, and 6 cases had a dose of 12 g/day.

5.2. Adverse Events

5.2.1. Brief Summary of Adverse Events

A summary of adverse events is shown in Table 3.1.

Adverse events occurred in all subjects. There were no deaths. Serious adverse events occurred twice in 2 cases. Among them, an increase in blood creatine phosphokinase and gastroenteritis occurred once each in 1 subject. There were no adverse events judged as severe or adverse events that resulted in withdrawal from the trial. The results were shown in Table 4.3.1-1-3.

Table 3.1 Summary of Adverse Events (Safety Analysis)

Item	Total Cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Adverse events	10 (100.0)	1 (100.0)	9 (100.0)
Serious adverse events	2 (20.0)	0 (0.0)	2 (22.2)
Dead case	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Severity [1)]			
mild	5 (50.0)	1 (100.0)	4 (44.4)
moderate	5 (50.0)	0 (0.0)	5 (55.6)
severe	0 (0.0)	0 (0.0)	0 (0.0)
Relationship with taurine [2)]			
No	4 (40.0)	0 (0.0)	4 (44.4)
Yes	6 (60.0)	1 (100.0)	5 (55.6)

Quoted from Table 4.3.1-1

When multiple adverse events were observed in the same subject, adverse events with the highest severity were counted.

5.2.2. Display of Adverse Events

Table 3.2 and Table 3.3 show the frequency of occurrence of adverse events broken down by SOC, PT and severity, and the frequency of occurrence of side effects broken down by SOC, PT and severity, respectively.

Adverse events that occurred in more than 2 cases included 5 cases of nasopharyngitis, 4 cases of diarrhea, 3 cases of increased blood creatine phosphokinase, and 2 cases each of leukocytosis, otalgia, vomiting, fever, influenza, contusion, C-reactive protein elevation, increase in γ-glutamyl transferase and increase in neutrophil count.

The following side effects were each observed once: constipation, diarrhea, gastroesophageal reflux disease, hiatal hernia, stomatitis, gastroenteritis, increased γ-glutamyl transferase, decreased appetite, insomnia, and frequent urination.

Table 3.2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total Cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Adverse event	-	10 (100.0)	1 (100.0)	9 (100.0)
Blood and lymphatic system disorders		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Leukocytosis		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Ear and labyrinthine disorders		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Otalgia		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Ocular disorder		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Allergic conjunctivitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Gastrointestinal problems		7 (70.0)	1 (100.0)	6 (66.7)
	mild	6 (60.0)	1 (100.0)	5 (55.6)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Diarrhea		4 (40.0)	1 (100.0)	3 (33.3)
	mild	4 (40.0)	1 (100.0)	3 (33.3)
Vomiting		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Stomachache		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Epigastric pain		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

Table 3.2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total Cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Constipation		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Gastritis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Reflux esophagitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Hiatal hernia		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Stomatitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Toothache		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
General・general disability and state of administration site		3 (30.0)	0 (0.0)	3 (33.3)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Fever		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Fatigue		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Infectious diseases and parasitic diseases		7 (70.0)	0 (0.0)	7 (77.8)
	mild	4 (40.0)	0 (0.0)	4 (44.4)
	moderate	3 (30.0)	0 (0.0)	3 (33.3)
Nasopharyngeitis		5 (50.0)	0 (0.0)	5 (55.6)
	mild	3 (30.0)	0 (0.0)	3 (33.3)
	moderate	2 (20.0)	0 (0.0)	2 (22.2)
Influenza		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Gastroenteritis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Viral gastroenteritis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Gingivitis		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)

Table 3.2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total Cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Herpes zoster		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Rhinitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Tinea infection		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Injury, poisoning and treatment complications		3 (30.0)	0 (0.0)	3 (33.3)
	mild	3 (30.0)	0 (0.0)	3 (33.3)
Contusion		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Ligament sprain		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Lumbar puncture syndrome		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Peel fracture		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Laboratory test		6 (60.0)	0 (0.0)	6 (66.7)
	mild	4 (40.0)	0 (0.0)	4 (44.4)
	moderate	2 (20.0)	0 (0.0)	2 (22.2)
Serum creatine kinase elevation		3 (30.0)	0 (0.0)	3 (33.3)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
C-reactive protein elevation		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Increase of γ-glutamyl transferase		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Increase in neutrophil count		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Alanine aminotransferase increase		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

Table 3.2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] / PT[1)]	Severity[2)]	Total Cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Aspartate aminotransferase increase		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Increase blood lactate dehydrogenase		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Increase in blood potassium		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Blood triglyceride increase		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Heart rate increase		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Lymphocyte count reduction		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Increase in white blood cell count		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Metabolism and malnutrition		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Dehydration		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Appetite loss		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Musculoskeletal system and connective tissue disorder		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Arthralgia		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Arthritis		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Limb pain		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Disorder of nervous system		3 (30.0)	0 (0.0)	3 (33.3)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)

Table 3.2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total Cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Convulsion		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Headache		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Post herpetic neuralgia		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Mental disorder		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Auditory hallucination		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Sleepless		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Renal and urinary tract disorder		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Urinary frequency		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Respiratory, thoracic and mediastinal disorders		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Aspiration pneumonia		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Inflammation of upper respiratory tract		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Skin and subcutaneous tissue injury		3 (30.0)	0 (0.0)	3 (33.3)
	mild	3 (30.0)	0 (0.0)	3 (33.3)
Keloid scar		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Rash		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Hand dermatitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

Quoted from Table 4.3.1-2

1) MedDRA Ver. 17.1 was used.

2) When multiple adverse events were observed in the same sujects in the same SOC and the same PT, the most severe adverse events were counted.

Table 3.3 Frequency of Side Effects by SOC, PT and Severity (Safety Analysis)

SOC[1)] / PT[1)]	Severity[2)]	Total Cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Side effects	-	6 (60.0)	1 (100.0)	5 (55.6)
Gastrointestinal disorder		3 (30.0)	1 (100.0)	2 (22.2)
	mild	3 (30.0)	1 (100.0)	2 (22.2)
Constipation		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Diarrhea		1 (10.0)	1 (100.0)	0 (0.0)
	mild	1 (10.0)	1 (100.0)	0 (0.0)
Gastroesophageal reflux disease		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Hiatal hernia		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Stomatitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Infections and parasitosis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Gastroenteritis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Laboratory test		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Increase of γ-glutamyl transferase		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Metabolism and nutritional disorders		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Appetite loss		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Mental disorder		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Sleepless		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

Table 3.3 Frequency of Side Effects by SOC, PT and Severity (Safety Analysis)

SOC[1)] / PT[1)]	Severity[2)]	Total Cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Renal and urinary tract disorder		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Urinary frequency		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

Quoted from Table 4.3.1-3

1) MedDRA Ver. 17.1 was used.

2) When multiple adverse events were observed in the same sujects in the same SOC and the same PT, the most severe adverse events were counted.

5.2.3. Analysis of Adverse Events

5.2.3.1. Adverse Events by Severity

Adverse events judged moderate included 2 cases of nasopharyngitis, and 1 case each of otolagia, vomiting, fever, gingivitis, shingles, increased blood creatine phosphokinase, increased C-reactive protein, increased blood lactate dehydrogenase, arthritis, post-herpetic neuralgia, and inflammation of the upper respiratory tract. All remaining adverse events were judged to be mild, and there were no adverse events judged to be severe.

5.2.3.2. Adverse Events by Causal Relationship

The following side effects were each observed once: constipation, diarrhea, gastroesophageal reflux disease, hiatal hernia, stomatitis, gastroenteritis, increase in γ-glutamyl transferase, appetite loss, sleepless, and urinary frequency. All of their severities were judged to be mild.

5.2.4. List of Adverse Events for Each Subject

A list of adverse events for each subject is tabulated

5.3. Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

5.3.1. List of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

5.3.1.1. Deaths

No deaths were observed in this trial.

5.3.1.2. Other Serious Adverse Events

A list of serious adverse events is shown in Table 3.4.

Serious adverse events were increase in blood creatine phosphokinase and gastroenteritis, and each occurred once in 1 subject.

Table 3.4 Serious Adverse Event List (Safety Analysis Group)

Subject identification number, without・with the co-administration of L-arginine/

Name of adverse event described by doctor (SOC[1)]/PT[1)])	Date of occurrence	Date of resolution	Period of occurrence (day)[2)]	Degree of seriousness	Breakdown of seriousness[3)]	Severity	Treatment	Outcome	Measures for investigational drugs	Relationship with taurine	Comment
KN-03-01, with the co-administration of L-arginine											
Serum CK elevation (Laboratory test/ increase in blood creatine phosphokinase)	2014/04/18	2014/05/20	33	serious	3	moderate	none	Recovery	continued	No	symptoms caused by MELAS
KN-10-01, with the co-administration of L-arginine											
Acute Gastroenteritis (Infectious diseases and parasitic diseases/ Gastroenteritis)	2014/04/10	2014/05/19	40	serious	3	mild	drug treatment	Recovery	continued	No	Infection

Quoted from Table 4.3.2-2

1）MedDRA Ver.17.1 were used.

2）Outcome data – Appearance date + 1

3) 1: death, 2:threaterned to death, 3: hospital or clinic hospitalization for treatment or extension of hospitalization period (excluding examination hospitalization), 4: Failure, 5: things that may lead to disability, those that are serious according to the cases listed in 6: 1 to 5, 7: congenital diseases or abnormalities in the later generations.

Other Significant Adverse Events

No adverse event occurred that resulted in discontinuation of administration.

5.3.2. Description of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Serious Adverse Events

The results are shown in Table 4.3.2-2.

Subject identification code: KN-03-01 Gender / Age: Male / 24 years old
Name of Serious adverse event: Physician description: rise in CK, MedDRA/ J PT: increased blood creatine phosphokinase Severity: Moderate Outcome: Recovery Clinical trial continuation or withdrawal: Continuation Causal relationship with investigational drugs: None

Subject Background

This subject was a 24-year old male, diagnosed with MELAS, and there were no complications. The drugs being used when the severe adverse events presented were Tegretol (tablet), Famotidine (tablet), Nauzerin (tablet), and Argi U blended granules.

Course and Causal Relationship with the Investigational Drug

The case received the first dose of the investigational drug on January 7, 2014. A head MRI was taken on April 18, 2014, and a new lesion was confirmed in the right temporal lobe, leading to emergency hospitalization. On April 22, 2014, a high vibration delta wave was observed in area of the lesion, and the next day, CK increased to 8,207 U/L, and Fostoin IV drip was begun. CK improved to 1,709 U/L on April 25, 2014, but a head MRI revealed an enlargement of the lesion in the right occipital and temporal lobes, and edema was observed at the same sites, so 1000 mg of steroid pulse was delivered. Cerebral edema slightly improved on May 2, 2014, and the next day, CK normalized to 109 U/L.

Because this event involved hospitalization for treatment, it was judged to be severe by the investigator. Elevated CK was thought to be caused by non-convulsive epilepsy, and it was judged that there was no causal relation with the investigational drug.

Subject identification code: KN-10-01 Gender / Age: Male / 15 years old
Serious adverse event name: Physician description: Acute gastroenteritis, MedDRA /J PT: Gastroenteritis Severity: Mild Outcome: Recovery Clinical trial continuation or withdrawal: Continuation Causal relationship with investigational drugs: None

Subject Background

This case was a 15-year old male, diagnosed with MELAS, and there were no complications. The drugs being used when the severe adverse events presented were Alinamin F (tablet), Urinmet combination (tablet), Tegretol fine granules, Neuquinon (tablet), Levocarnitine (tablet), Magnesium oxide, Thyradin S (tablet), Levetiracetam (tablet), Argi U combination granules, Diazepam (tablet), Acetaminophen (tablet).

Course and Causal Relationship with the Investigational Drug

The case received the first dose of the investigational drug on November 7, 2014. When being examined on April 11, 2014, the subject presented sustained, frequent watery stools, strong malaise, and dehydration, and was hospitalized for transfusion. He was discharged on April 17, 2014 with good overall condition. On May 15, 2014, he presented with headache and vomiting, with the diagnosis that there was a possibility of a MELAS attack, and was admitted to the hospital. The next day, a new lesion was confirmed in the right temporal region by head MRI. On May 19, 2014, the acute gastroenteritis was judged to have recovered.

Because this event involved hospitalization for treatment, it was judged to be severe by the investigator. It was considered to possibly be diarrhea caused by infection, effects of MELAS symptoms, and the improvement of intestinal function, and it was judged that there was no causal relation with the investigational drug.

5.3.3. Analysis and Discussion of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Serious adverse events other than death occurred twice in 2 cases. Specifically, increased blood creatine phosphokinase and gastroenteritis each occurred once in 1 case. Increased blood creatine phosphokinase was thought to be caused by non-convulsive epilepsy, and it was judged that there was no causal relation with the investigational drug. In addition, the gastroenteritis was considered to possibly be diarrhea caused by infection, effects of MELAS symptoms, and the improvement of

intestinal function, and it was judged that there was no causal relation with the investigational drug. No adverse event occurred that resulted in discontinuation of administration.

5.4. Evaluation of Clinical Examination Items

5.4.1. Clinical Examination Values throughout the Trial Period

Lists for each subject: hematological examination, biochemical examination, blood amino acid analysis, cerebrospinal fluid amino acid analysis, and blood leukocyte examination were tabulated in Table 4.3.4-3 - Table 4.3.4-7.

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5.4.2. Evaluation of Clinical Examination Items

5.4.2.1. Clinical Examination Values throughout the Trial Period

Trends in hematological examination and biochemical examination were shown in Table 4.3.4-1 and Table 4.3.4-2.

5.4.2.2. Changes in Individual Subjects

Trends in hematological examination and biochemical examination were tabulated in Table 4.3.4-3 - Table 4.3.4-7.

5.4.2.3. Clinically Significant Individual Abnormalities

Abnormal fluctuation was observed in 2 cases of increased blood creatine phosphokinase, 2 cases each of increased γ-glutamyl transferase and increased neutrophils, and 1 case each of reduced lymphocyte count and increased leukocyte count. All of these were judged to be adverse events. In addition, although 1 case of increased blood creatine phosphokinase was recognized as abnormal, it was not recognized as abnormal fluctuation, but rather was judged to be an adverse event. One case of increased blood creatine phosphokinase was judged to be a severe adverse event, but it was concluded that it had no relationship with the investigational drug, and the subject recovered without treatment. In addition, one case of increased γ-glutamyltransferase was judged to be a side effect, but the severity was mild and the subject recovered with no treatment.

5.5. Vital Signs, Physical Findings, and Other Observations Related to Safety

5.5.1. Physical Examinations

Lists broken down by physical examination item at each measurement time are shown in Table 4.3.5-1 and Table 4.3.5-2.

These abnormal fluctuations were found: 1 case of increased heart rate, and 2 cases of fever. Among them, 1 case of increased heart rate and 1 case of fever were judged to be adverse events.

The 1 case of increased heart rate and 1 case of fever occurred in the same subject, and it was concluded that these had no relationship with the investigational drug.

There were no noticeable changes observed on the whole.

5.6. Conclusion of Safety

Adverse events occurred in all the cases. No deaths were observed. Serious adverse events occurred twice in 2 cases. Among them, an increase in blood creatine phosphokinase and gastroenteritis occurred once each in 1 subject. Adverse events judged as severe and adverse events leading to discontinuation were not observed.

Adverse events that occurred in 2 cases or more included 5 cases of nasopharyngitis, 4 cases of diarrhea, 3 cases of increased blood creatine phosphokinase, and 2 cases each of leukocytosis, otolaigia, vomiting, fever, influenza, contusion, increase in C-reactive protein, increase in γ-glutamyl transferase, and increase in neutrophil count.

The following side effects were each observed once: constipation, diarrhea, gastroesophageal reflux disease, hiatal hernia, stomatitis, gastroenteritis, increased γ-glutamyl transferase, decreased appetite, insomnia, and frequent urination.

Adverse events judged moderate included 2 cases of nasopharyngitis, and 1 case each of earache, vomiting, fever, gingivitis, shingles, increased blood creatine phosphokinase, increased C-reactive protein, increased blood lactate dehydrogenase, arthritis, post-herpetic neuralgia, and inflammation of the upper respiratory tract. All remaining adverse events were judged to be mild, and there were no adverse events judged to be severe.

Serious adverse events occurred twice in 2 cases. Specifically, increased blood creatine phosphokinase and gastroenteritis each occurred once in 1 subject. Both of them were judged not to be related to the investigational drug. No adverse event occurred that resulted in discontinuation of administration.

6. Discussion and General Conclusion

The efficacy and safety of taurine administered in doses by weight category to 10 patients with MELAS for 52 weeks for the purpose of suppressing the recurrence of stroke-like episodes was verified.

The percentage of subjects that attained the primary endpoint, 0 stroke-like episodes, was 60% (6/10 subjects) (100% responders). The lower limit of the 95% confidence interval was 26.2% in all the cases and 21.1% in L-arginine Co-administration cases, which was significantly higher than the threshold responder rate set in the trial protocol; clinical efficacy was verified. The 50% responder rate, the secondary endpoints, also showed a high value of 80% (8/10 subjects). The maximum number of administrations of L-arginine intravenous formulation per single episodes was 14 before

investigational drug administration, but it decreased to 7 after administration. Symptoms other than abrupt-onset neurological deficits were observed after investigational drug administration twice in 2 subjects, with 1 subject having 1 case of headache, and the other subject having 1 case of headache and nausea/vomiting.

Adverse events occurred in all the cases, but no severe events were observed, and recovery was generally observed. Although severe adverse events, that is, increased blood creatine phosphokinase and gastroenteritis, were observed in 2 subjects, they were mild and their degree was moderate, and it was concluded that they were not related to the investigational drug. As for the safety of the investigational drug, given that there were no adverse events that prevented the continuation of the clinical trial, and that the investigational drug administration continued through the last observation day in Week 52 for all registered subjects (10 subjects), it is considered that its safety was confirmed.

Thus, the efficacy and safety of the investigational drug in suppressing recurrence of stroke-like attacks in MELAS patients was demonstrated.

7. Tables to be quoted

Table 4.1-1 Breakdown of subjects

Breakdown of subjects	Total cases n (%)	No L-arginine Co-Administration cases n (%)	L-arginine Co-Administration cases n (%)
Cases with acquired consent			
Number of the Subjects	10	1	9
Enrolled subjects			
Number of the Subjects	10 (100.0)	1 (100.0)	9 (100.0)
Subjects omitted before enrollment			
Number of the Subjects	0	0	0
Full Analysis Set (FAS)			
Used	10 (100.0)	1 (100.0)	9 (100.0)
Not Used	0 (0.0)	0 (0.0)	0 (0.0)
Per Protocol Set (PPS)			
Used	10 (100.0)	1 (100.0)	9 (100.0)
Not Used	0 (0.0)	0 (0.0)	0 (0.0)
Safety analysis population			
Used	10 (100.0)	1 (100.0)	9 (100.0)
Not Used	0 (0.0)	0 (0.0)	0 (0.0)

Program Name: T050101.sas / Output: t050101.rtf
Date of Table Generation: 2015-02-18 21:10
Data Source: adec

Table 4.1-2 Frequency of the study completion and withdrawal by each by reason of discontinuation (Enrolled subjects)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Completed cases	10 (100.0)	1 (100.0)	9 (100.0)
Discontinued cases	0 (0.0)	0 (0.0)	0 (0.0)
①Case with withdrawal of consent from subject or substitute	0 (0.0)	0 (0.0)	0 (0.0)
②Case in which subjects or prosecutors requested change or discontinuation of treatment	0 (0.0)	0 (0.0)	0 (0.0)
③Case in which the investigational responsibility (shared) doctor judged that the continuation of the trial was inappropriate due to the occurrence of an adverse event (worsening complications, complication of new diseases, etc.)	0 (0.0)	0 (0.0)	0 (0.0)
④Case in which investigational responsibility (shared) doctor judged that continuation of the clinical trial is not appropriate due to deterioration of the original disease	0 (0.0)	0 (0.0)	0 (0.0)
⑤Case where you can not go to the hospital on the visit date determined by the move etc.	0 (0.0)	0 (0.0)	0 (0.0)
⑥Case in which the subject was found to be pregnant	0 (0.0)	0 (0.0)	0 (0.0)
⑦Case where conflicts with selection criteria or conflicts with exclusion criteria were found	0 (0.0)	0 (0.0)	0 (0.0)
⑧Case where a serious deviation from the protocol was confirmed	0 (0.0)	0 (0.0)	0 (0.0)
⑨Others, such as a case in which the investigational responsibility (shared) doctor judged that continuation of the trial is inappropriate	0 (0.0)	0 (0.0)	0 (0.0)

Program Name: T050102.sas / Output: t050102.rtf
Date of Table Generation: 2015-02-18 21:10
Data Source: adds

Table 4.1-3 Characteristics of demographic and other reference values (FAS)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Gender: n (%)			
Male	7 (70.0)	1 (100.0)	6 (66.7)
Female	3 (30.0)	0 (0.0)	3 (33.3)
Age at consent acquisition (y)			
Number of cases	10	1	9
Mean	29.1	31.0	28.9
SD	11.49	-	12.17
Median, Minimum, Maximum	30.0, 14, 46	-, -, -	30.0, 14, 46
Age at consent acquisition: n (%)			
10-<20 y	3 (30.0)	0 (0.0)	3 (33.3)
20-<30 y	1 (10.0)	0 (0.0)	1 (11.1)
30-<40 y	4 (40.0)	1 (100.0)	3 (33.3)
40-<50 y	2 (20.0)	0 (0.0)	2 (22.2)
Number of stroke-like-episodes within the 78 weeks period before consent: n (%)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)
2	4 (40.0)	0 (0.0)	4 (44.4)
3	2 (20.0)	1 (100.0)	1 (11.1)
4	4 (40.0)	0 (0.0)	4 (44.4)
The use of intravenous L-arginine administration within the 78 weeks period before consent: n (%)			
No	2 (20.0)	1 (100.0)	1 (11.1)
Yes	8 (80.0)	0 (0.0)	8 (88.9)
Point mutation of mitochondrial DNA at position 3243 (A3243G): n (%)			
No	1 (10.0)	1 (100.0)	0 (0.0)
Yes	9 (90.0)	0 (0.0)	9 (100.0)

1) Evaluation period of stroke-like episodes before starting the trial
2) High signal confirmation by MRI is not indispensable for the stroke-like- episodes, since the evaluation period of a stroke-like-episode is before the start of the trial.

Program Name: T06.sas / Output: t06_f.rtf
Date of Table Generation: 2015-02-18 21:10 Data Source: addm

Table 4.1-3 Characteristics of demographic and other reference values (FAS)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Mitochondrial DNA point mutation: T3271C: n (%)			
No	9 (90.0)	0 (0.0)	9 (100.0)
Yes	1 (10.0)	1 (100.0)	0 (0.0)
Mitochondrial DNA point mutation: G3244A n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Mitochondrial DNA point mutation: T3258C n (%)			
No	10 (100.0)	0 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Mitochondrial DNA point mutation: T3291C n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Systolic BP (mmHg)			
N	10	1	9
Mean	119.7	124.0	119.2
SD	13.77	-	14.52
Median, Minimum, Maximum	119.5, 100, 147	-, -, -	115.0, 100, 147
Diastolic BP (mmHg)			
N	10	1	9
Mean	73.5	65.0	74.4
SD	12.94	-	13.35
Median, Minimum, Maximum	72.5, 52, 93	-, -, -	74.0, 52, 93
Pulse (beats/min)			
N	10	1	9
Mean	86.3	111.0	83.6
SD	15.68	-	13.86
Median, Minimum, Maximum	86.5, 64, 111	-, -, -	83.0, 64, 106

1) Evaluation period of stroke-like episodes before starting the trial
2) High signal confirmation by MRI is not indispensable for the stroke-like- episodes, since the evaluation period of a stroke-like-episode is before the start of the trial.

Program Name: T06.sas / Output: t06_f.rtf
Date of Table Generation: 2015-02-18 21:10
Data Source: addm

Table 4.1-3 Characteristics of demographic and other reference values (FAS)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Height (cm)			
N	10	1	9
Mean	155.43	172.00	153.59
SD	10.208	-	8.894
Median, Minimum, Maximum	154.80,140.3,172.0	-, -, -	153.40,140.3,169.9
Body weight (kg)			
N	10	1	9
Mean	41.94	41.40	42.00
SD	8.346	-	8.850
Median, Minimum, Maximum	41.60, 32.0, 59.4	-, -, -	41.80, 32.0, 59.4
Body weight: n (%)			
<15kg	0 (0.0)	0 (0.0)	0 (0.0)
15-<25kg	(0.0)	0 (0.0)	0 (0.0)
25-<40kg	4 (40.0)	0 (0.0)	4 (44.4)
40- kg	6 (60.0)	1 (100.0)	5 (55.6)
Complications: n (%)			
No	2 (20.0)	0 (0.0)	2 (22.2)
Yes	8 (80.0)	1 (100.0)	7 (77.8)
Smoking: n (%)			
No	2 (20.0)	0 (0.0)	2 (22.2)
Yes	8 (80.0)	1 (100.0)	7 (77.8)
No smoking episode	8 (80.0)	1 (100.0)	7 (77.8)
Current Smoker	0 (0.0)	0 (0.0)	0 (0.0)
Previous smoker	2 (20.0)	0 (0.0)	2 (22.2)
Complications within the 78 weeks period before consent: n (%)			
No	8 (80.0)	1 (100.0)	7 (77.8)
Yes	2 (20.0)	0 (0.0)	2(22.2)

1) Evaluation period of stroke-like episodes before starting the trial
2) High signal confirmation by MRI is not indispensable for the stroke-like- episodes, since the evaluation period of a stroke-like-episode is before the start of the trial.

Program Name: T06.sas / Output: t06_f.rtf
Date of Table Generation: 2015-02-18 21:10
Data Source: addm

Table 4.1-4 Characteristics of demographic and other reference values (PPS)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Gender: n (%)			
Male	7 (70.0)	1 (100.0)	6 (66.7)
Female	3 (30.0)	0 (0.0)	3 (33.3)
Age at consent acquisition (y)			
Number of cases	10	1	9
Mean	29.1	31.0	28.9
SD	11.49	-	12.17
Median, Minimum, Maximum	30.0, 14, 46	-, -, -	30.0, 14, 46
Age at consent acquisition (y): n (%)			
10-<20 y	3 (30.0)	0 (0.0)	3 (33.3)
20-<30 y	1 (10.0)	0 (0.0)	1 (11.1)
30-<40 y	4 (40.0)	1(100.0)	3 (33.3)
40-<50	2 (20.0)	0 (0.0)	2 (22.2)
Number of stroke-like-episodes within the 78 weeks period before consent: n (%)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)
2	3 (40.0)	0 (0.0)	4 (44.4)
3	2 (20.0)	1 (100.0)	1 (11.1)
4	4 (40.0)	0 (0.0)	4 (44.4)
The use of intravenous L-arginine administration within the 78 weeks period before consent: n (%)			
No	2 (20.0)	1 (100.0)	1 (11.1)
Yes	8 (80.0)	0 (0.0)	8 (88.9)
Point mutation of mitochondrial DNA at position 3243 (A3243G): n (%)			
No	1 (10.0)	1(100.0)	0 (0.0)
Yes	9 (90.0)	0 (0.0)	9 (100.0)

1) Evaluation period of stroke-like episodes before starting the trial
2) High signal confirmation by MRI is not indispensable for the stroke-like- episodes, since the evaluation period of a stroke-like-episode is before the start of the trial.

Program Name: T06.sas / Output: t06_p.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: addm

Table 4.1-4 Characteristics of demographic and other reference values (PPS)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Mitochondrial DNA point mutation: T3271C n (%)			
No	9 (90.0)	0 (0.0)	9 (100.0)
Yes	1 (10.0)	1 (100.0)	0 (0.0)
Mitochondrial DNA point mutation: G3244A n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Mitochondrial DNA point mutation: T3258C n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Mitochondrial DNA point mutation: T3291C n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Systolic BP (mmHg)			
N	10	1	9
Mean	119.7	124.0	119.2
SD	13.77	-	14.52
Median, Minimum, Maximum	119.5, 100, 147	-, -, -	115.0, 100, 147
Diastolic BP (mmHg)			
N	10	1	9
Mean	73.5	65.0	74.4
SD	12.94	-	13.35
Median, Minimum, Maximum	72.5, 52, 93	-, -, -	74.0, 52, 93
Pulse (beats/min)			
N	10	1	9
Mean	86.3	111.0	83.6
SD	15.68	-	13.86
Median, Minimum, Maximum	86.5, 64, 111	-, -, -	83.0, 64, 106

1) Evaluation period of stroke-like episodes before starting the trial
2) High signal confirmation by MRI is not indispensable for the stroke-like- episodes, since the evaluation period of a stroke-like-episode is before the start of the trial.

Program Name: T06.sas / Output: t06_p.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: addm

Table 4.1-4 Characteristics of demographic and other reference values (PPS)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Height (cm)			
N	10	1	9
ME	155.43	172.00	153.59
SD	10.208	-	8.894
Median, Minimum, Maximum	154.80,140.3,172.0	-, -, -	153.40,140.3,169.9
Body weight (kg)			
N	10	1	9
Mean	41.94	41.40	42.00
SD	8.346	-	8.850
Median, Minimum, Maximum	41.60, 32.0, 59.4	-, -, -	41.80, 32.0, 59.4
Body weight: n (%)			
<15kg	0 (0.0)	0 (0.0)	(0.0)
15-<25kg	0 (0.0)	0 (0.0)	(0.0)
25-<40kg	4(40.0)	0 (0.0)	(44.4)
40- kg	6 (60.0)	1 (100.0)	5 (55.6)
Complications: n (%)			
No	2 (20.0)	0 (0.0)	2 (22.2)
Yes	8 (80.0)	1 (100.0)	7 (77.8)
Smoking: n (%)			
No smoking episode	8 (80.0)	1 (100.0)	7 (77.8)
Current smoker	0 (0.0)	0 (0.0)	0 (0.0)
Previous smoker	2 (20.0)	0 (0.0)	2 (22.2)
Complications within the 78 weeks period before consent: n (%)			
No	8 (80.0)	1 (100.0)	7 (77.8)
Yes	2 (20.0)	0 (0.0)	2 (22.2)

1) Evaluation period of stroke-like episodes before starting the trial
2) High signal confirmation by MRI is not indispensable for the stroke-like- episodes, since the evaluation period of a stroke-like-episode is before the start of the trial.

Program Name: T06.sas / Output: t06_p.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: addm

Table 4.1-5 Characteristics of demographic and other reference values (Safety Analysis)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Gender: n (%)			
Male	7 (70.0)	1 (100.0)	6 (66.7)
Female	3 (30.0)	0 (0.0)	3 (33.3)
Age at consent acquisition (y)			
Number of cases	10	1	9
Mean	29.1	31.0	28.9
SD	11.49	-	12.17
Median, Minimum, Maximum	30.0, 14, 46	-, -, -	30.0, 14, 46
Age at consent acquisition (y): n (%)			
10-<20 y	3 (30.0)	0 (0.0)	3 (33.3)
20-<30 y	1 (10.0)	0 (0.0)	1 (11.1)
30-<40 y	4 (40.0)	1 (100.0)	3 (33.3)
40-<50 y	2 (20.0)	0 (0.0)	2 (22.2)
Number of stroke-like-episodes within the 78 weeks period before consent: n (%)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)
2	4 (40.0)	0 (0.0)	4 (44.4)
3	2 (20.0)	1 (100.0)	1 (11.1)
4	4 (40.0)	0 (0.0)	4 (44.4)
The use of intravenous L-arginine administration within the 78 weeks period before consent: n (%)			
No	2 (20.0)	1 (100.0)	1 (11.1)
Yes	8 (80.0)	0 (0.0)	8 (88.9)
Point mutation of mitochondrial DNA at position 3243 (A3243G): n (%)			
No	1 (10.0)	1 (100.0)	0 (0.0)
Yes	9 (90.0)	0 (0.0)	9 (100.0)

1) Evaluation period of stroke-like episodes before starting the trial
2) High signal confirmation by MRI is not indispensable for the stroke-like- episodes, since the evaluation period of a stroke-like-episode is before the start of the trial.

Program Name: T06.sas / Output: t06_s.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: addm

Table 4.1-5 Characteristics of demographic and other reference values (Safety Analysis)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Mitochondrial DNA point mutation: T3271 n (%)			
No	9 (90.0)	0 (0.0)	9 (100.0)
Yes	1 (10.0)	1 (100.0)	0 (0.0)
Mitochondrial DNA point mutation: G3244A: n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Mitochondrial DNA point mutation: T3258C n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Mitochondrial DNA point mutation: T3291C n (%)			
No	10 (100.0)	1 (100.0)	9 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)
Systolic BP (mmHg)			
N	10	1	9
Mean	119.7	124.0	119.2
SD	13.77	-	14.52
Median, Minimum, Maximum	119.5, 100, 147	-, -, -	115.0, 100, 147
Diastolic BP (mmHg)			
N	10	1	9
Mean	73.5	65.0	74.4
SD	12.94	-	13.35
Median, Minimum, Maximum	72.5, 52, 93	-, -, -	74.0, 52, 93
Pulse (beats/min)			
N	10	1	9
Mean	86.3	111.0	83.6
SD	15.68	-	13.86
Median, Minimum, Maximum	86.5, 64, 111	-, -, -	83.0, 64, 106

1) Evaluation period of stroke-like episodes before starting the trial
2) High signal confirmation by MRI is not indispensable for the stroke-like- episodes, since the evaluation period of a stroke-like-episode is before the start of the trial.

Program Name: T06.sas / Output: t06_s.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: addm

Table 4.1-5 Characteristics of demographic and other reference values (Safety Analysis)

	Total cases N=10	No L-arginine Co-Administration cases N=1	L-arginine Co-Administration cases N=9
Height (cm)			
N	10	1	9
Mean	155.43	172.00	153.59
SD	10.208	-	8.894
Median, Minimum, Maximum	154.80,140.3,172.0	-, -, -	153.40,140.3,169.9
Body weight (kg)			
N	10	1	9
Mean	41.94	41.40	42.00
SD	8.346	-	8.850
Median, Minimum, Maximum	41.60, 32.0, 59.4	-, -, -	41.80, 32.0, 59.4
Body weight: n (%)			
<15kg	0 (0.0)	0 (0.0)	0 (0.0)
15-<25kg	0 (0.0)	0 (0.0)	0 (0.0)
25-<40kg	4 (40.0)	0 (0.0)	4 (44.4)
40- kg	6 (60.0)	1 (100.0)	5 (55.6)
Complications: n (%)			
No	2 (20.0)	0 (0.0)	2 (22.2)
Yes	8 (80.0)	1 (100.0)	7 (77.8)
Smoking: n (%)			
No smoking episode	8 (80.0)	1 (100.0)	7 (77.8)
Current smoker	0 (0.0)	0 (0.0)	0 (0.0)
Previous smoker	2 (20.0)	0 (0.0)	2 (22.2)
Complications within the 78 weeks period before consent: n (%)			
No	8 (80.0)	1 (100.0)	7 (77.8)
Yes	2 (20.0)	0 (0.0)	2 (22.2)

1) Evaluation period of stroke-like episodes before starting the trial
2) High signal confirmation by MRI is not indispensable for the stroke-like- episodes, since the evaluation period of a stroke-like-episode is before the start of the trial.

Program Name: T06.sas / Output: t06_s.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: addm

Table 4.2-1 Primary endpoint of the efficacy: 100% responder rate (FAS)

	Total cases N = 10	No L-arginine Co-Administration cases N = 1	L-arginine Co-Administration cases N = 9
No stroke-like episodes during the evaluation period: n (%)	6 (60.0)	1 (100.0)	5 (55.6)
Clopper-Pearson exact 95% confidential interval	26.2, 87.8	2.5, 100.0	21.2, 86.3

Program Name: T0701_01.sas / Output: t0701_01_f.rtf
Date of Table Generation: 2015-02-17 20:41
Data Source: adatt

Table 4.2-2 Primary endpoint of the efficacy: 100% responder rate (PPS)

	Total cases N = 10	No L-arginine Co-Administration cases N = 1	L-arginine Co-Administration cases N = 9
No stroke-like episodes during the evaluation period: n (%)	6 (60.0)	1 (100.0)	5 (55.6)
Clopper-Pearson exact 95% confidential interval	26.2, 87.8	2.5, 100.0	21.2, 86.3

Program Name: T0701_01.sas / Output: t0701_01_p.rtf
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Data Source: adatt6

Table 4.2-3 Primary endpoint of the efficacy - 100% responder rate Logistic regression No.1 (FAS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Gender			
Male against Female	0.111	0.003～4.646	0.2487
Age at consent acquisition			
+10 years old	1.543	0.456～5.219	0.4858
Frequency of stroke-like-episodes in the 78 weeks before acquiring consent[1), 2)]			
+1 time	1.000	0.245～4.078	1.0000
Complications			
'None' against 'Present'	13.003	0.232～730.120	0.2120
Smoking history			
'Current smoker' against 'No smoking episode'	N/A	N/A	N/A
'Previous smoker' against 'No smoking episode'	0.200	0.004～10.583	0.4267
Past medical history in the 78 weeks period before acquiring consent[1), 2)]			
'None' against 'Present'	5.002	0.094～264.732	0.4267
Blood taurine concentration (Week 0)			
+100nmol/mL	5.375	0.005～>999.999	0.6351
Blood taurine concentration (Week 52 or when canceled)			
+100nmol/mL	1.000	0.720～1.389	1.0000
L-arginine in blood (Week 0)			
+100nmol/mL	0.328	0.049～2.175	0.2480
L-arginine in blood (Week 52 or when canceled)			
+100nmol/mL	0.702	0.165～2.983	0.6317
Lactate in blood (Week 0)			
+10mg/dL	1.409	0.436～4.553	0.5667
Lactate in blood (Week 52 or when canceled)			
+10mg/dL	1.485	0.491～4.488	0.4837

1) Evaluation period of stroke-like episodes before starting the trial
2) 'Stroke-like-episodes' before the start of the trial are defined as 'abrupt-onset focal neurological deficits'.

Program Name: T0701_02_01_a.sas / Output: t0701_02_01_a_f.rtf
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Data Source: adatt6

Table 4.2-3 Primary endpoint of the efficacy - 100% responder rate Logistic regression No.1 (FAS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Lactate in CSF (Week 0)			
+10mg/dL	1.032	0.341～3.125	0.9557
Lactate in CSF (Week 52 or when canceled)			
+10mg/dL	1.033	0.400～2.666	0.9468
Pyruvate in blood (Week 0)			
+0.1mg/dL	1.122	0.780～1.613	0.5346
Pyruvate in blood (Week 52 or when canceled)			
+0.1mg/dL	1.175	0.868～1.591	0.2965
Pyruvate in CSF (Week 0)			
+0.1mg/dL	1.017	0.655～1.580	0.9391
Pyruvate in CSF (Week 52 or when canceled)			
+0.1mg/dL	0.985	0.709～1.368	0.9271
Lactate / Pyruvate ratio in blood (Week 0)			
+1	1.009	0.807～1.262	0.9358
Lactate / Pyruvate ratio in blood (Week 52 or when canceled)			
+1	0.942	0.716～1.240	0.6712
Lactate / Pyruvate ratio in CSF (Week 0)			
+1	1.002	0.710～1.414	0.9897
Lactate / Pyruvate ratio in CSF (Week 52 or when canceled)			
+1	1.043	0.723～1.503	0.8224
JMDRS (Week 0)			
+10	0.797	0.108～5.909	0.8245
JMDRS (Week 52 or when canceled)			
+10	0.490	0.099～2.428	0.3820

1) Evaluation period of stroke-like episodes before starting the trial
2) 'Stroke-like-episodes' before the start of the trial are defined as 'abrupt-onset focal neurological deficits'.

Program Name: T0701_02_01_a.sas / Output: t0701_02_01_a_f.rtf
Date of Table Generation: 2015-02-17 20:42
Data Source: adatt6

Table 4.2-4 Primary endpoint of the efficacy - 100% responder rate Logistic regression No.1 (PPS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Gender			
Male against Female	0.111	0.003～4.646	0.2487
Age at consent acquisition			
+10 years old	1.543	0.456～5.219	0.4858
Frequency of stroke-like-episodes in the 78 weeks before acquiring consent[1), 2)]			
+1time	1.000	0.245～4.078	1.0000
Complications			
'None' against 'Present'	13.003	0.232～730.120	0.2120
Smoking history			
'Current smoker' against 'No smoking episode'	N/A	N/A	N/A
'Previous smoker' against 'No smoking episode'	0.200	0.004～10.583	0.4267
Past medical history in the 78 weeks period before acquiring consent[1), 2)]			
'None' against 'Present'	5.002	0.094～264.732	0.4267
Blood taurine concentration (Week 0)			
+100nmol/mL	5.375	0.005～>999.999	0.6351
Blood taurine concentration (Week52 or when canceled)			
+100nmol/mL	1.000	0.720～1.389	1.0000
L-arginine in blood（Week 0）			
+100nmol/mL	0.328	0.049～2.175	0.2480
L-arginine in blood (Week 52 or when canceled)			
+100nmol/mL	0.702	0.165～2.983	0.6317
Lactate in blood (Week 0)			
+10mg/dL	1.409	0.436～4.553	0.5667
Lactate in blood (Week 52 or when canceled)			
+10mg/dL	1.485	0.491～4.488	0.4837

1) Evaluation period of stroke-like episodes before starting the trial
2) 'Stroke-like-episodes' before the start of the trial are defined as 'abrupt-onset focal neurological deficits'.

Program Name: T0701_02_01_a.sas / Output: t0701_02_01_a_p.rtf
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Data Source: adatt6

Table 4.2-4 Primary endpoint of the efficacy - 100% responder rate Logistic regression No.1 (PPS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Lactate in CSF (Week 0)			
+10mg/dL	1.032	0.341～3.125	0.9557
Lactate in CSF (Week 52 or when canceled)			
+10mg/dL	1.033	0.400～2.666	0.9468
Pyruvate in blood (Week 0)			
+0.1mg/dL	1.122	0.780～1.613	0.5346
Pyruvate in blood (Week 52 or when canceled)			
+0.1mg/dL	1.175	0.868～1.591	0.2965
Pyruvate in CSF (Week 0)			
+0.1mg/dL	1.017	0.655～1.580	0.9391
Pyruvate in CSF (Week 52 or when canceled)			
+0.1mg/dL	0.985	0.709～1.368	0.9271
Lactate / Pyruvate ratio in blood (Week 0)			
+1	1.009	0.807～1.262	0.9358
Lactate / Pyruvate ratio in blood (Week 52 or when canceled)			
+1	0.942	0.716～1.240	0.6712
Lactate / Pyruvate ratio in CSF (Week 0)			
+1	1.002	0.710～1.414	0.9897
Lactate / Pyruvate ratio in CSF (Week 52 or when canceled)			
+1	1.043	0.723～1.503	0.8224
JMDRS (Week 0)			
+10	0.797	0.108～5.909	0.8245
JMDRS (Week 52 or when canceled)			
+10	0.490	0.099～2.428	0.3820

1) Evaluation period of stroke-like episodes before starting the trial
2) 'Stroke-like-episodes' before the start of the trial are defined as 'abrupt-onset focal neurological deficits'.

Program Name: T0701_02_01_a.sas / Output: t0701_02_01_a_p.rtf
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Data Source: adatt6

Table 4.2-5 Primary endpoint of the efficacy - 100% responder rate Logistic regression No.2 (FAS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Mitochondrial DNA mutation rate (Week 0)			
+10%	0.765	0.296～1.976	0.5805
Mitochondrial DNA mutation rate (Week 52 or when canceled)			
+10%	0.817	0.330～2.021	0.6612
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 0)			
+0.1folds	0.995	0.962～1.029	0.7579
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 52 or when canceled)			
+0.1folds	0.998	0.988～1.009	0.7660
ND6 protein level (Week 0)			
+10pg/mL	0.148	<0.001～>999.999	0.8972
ND6 protein level (Week 52 or when canceled)			
+10pg/mL	119.133	<0.001～>999.999	0.7790

Program Name: T0701_02_02_a.sas / Output: t0701_02_02_a_f.rtf
Date of Table Generation: 2015-02-17 20:42
Data Source: adattsbl6

Table 4.2-6 Primary endpoint of the efficacy - 100% responder rate Logistic regression No.2 (PPS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Mitochondrial DNA mutation rate (Week 0)			
+10%	0.765	0.296～1.976	0.5805
Mitochondrial DNA mutation rate (Week 52 or when canceled)			
+10%	0.817	0.330～2.021	0.6612
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 0)			
+0.1folds	0.995	0.962～1.029	0.7579
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 52 or when canceled)			
+0.1folds	0.998	0.988～1.009	0.7660
ND6 protein level (Week 0)			
+10pg/mL	0.148	<0.001～>999.999	0.8972
ND6 protein level (Week 52 or when canceled)			
+10pg/mL	119.133	<0.001～>999.999	0.7790

Program Name: T0701_02_02_a.sas / Output: t0701_02_02_a_p.rtf
Date of Table Generation: 2015-02-17 20:42
Data Source: adattsbl6

Table 4.2-7 Primary endpoint of the efficacy - 50% responder rate Logistic regression No.1 (FAS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Gender			
Male against Female	0.314	0.007～13.722	0.5481
Age at consent acquisition			
+10 years old	0.796	0.212～2.986	0.7355
Frequency of stroke-like-episodes in the 78 weeks before acquiring consent[1), 2)]			
+1 time	4.117	0.429～39.484	0.2199
Complications			
'None' against 'Present'	5.001	0.178～140.786	0.3446
Smoking history			
'Current smoker' against 'No smoking episode'	N/A	N/A	N/A
'Previous smoker' against 'No smoking episode'	0.520	0.009～29.191	0.7503
Past medical history in the 78 weeks period before acquiring consent[1), 2)]			
'None' against 'Present'	1.923	0.034～107.990	0.7503
Blood taurine concentration (Week 0)			
+100nmol/mL	0.368	<0.001～538.335	0.7881
Blood taurine concentration (Week 52 or when canceled)			
+100nmol/mL	1.000	0.669～1.495	1.0000
L-arginine in blood（Week 0)			
+100nmol/mL	0.088	0.006～1.352	0.0812
L-arginine in blood (Week 52 or when canceled)			
+100nmol/mL	1.000	0.204～4.902	1.0000
Lactate in blood (Week 0)			
+10mg/dL	5.490	0.232～129.915	0.2915

1) Evaluation period of stroke-like episodes before starting the trial
2) 'Stroke-like-episodes' before the start of the trial are defined as 'abrupt-onset focal neurological deficits'.

Program Name: T0701_02_01_b.sas / Output: t0701_02_01_b_f.rtf
Date of Table Generation: 2015-02-17 20:42
Data Source: adatt6

Table 4.2-7 Primary endpoint of the efficacy - 50% responder rate Logistic regression No.1 (FAS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Lactate in blood (Week 52 or when canceled)			
+10mg/dL	4.546	0.476～43.434	0.1885
Lactate in CSF (Week 0)			
+10mg/dL	1.032	0.341～3.125	0.9557
Lactate in CSF(Week 52 or when canceled)			
+10mg/dL	1.033	0.400～2.666	0.9468
Pyruvate in blood (Week 0)			
+0.1mg/dL	1.050	0.707～1.559	0.8090
Pyruvate in blood (Week 52 or when canceled)			
+0.1mg/dL	1.337	0.796～2.245	0.2726
Pyruvate in CSF (Week 0)			
+0.1mg/dL	1.017	0.655～1.580	0.9391
Pyruvate in CSF (Week 52 or when canceled)			
+0.1mg/dL	0.985	0.709～1.368	0.9271
Lactate / Pyruvate ratio in blood (Week 0)			
+1	1.152	0.883～1.503	0.2958
Lactate / Pyruvate ratio in blood (Week 52 or when canceled)			
+1	1.125	0.796～1.590	0.5048
Lactate / Pyruvate ratio in CSF (Week 0)			
+1	1.002	0.710～1.414	0.9897
Lactate / Pyruvate ratio in CSF (Week 52 or when canceled)			
+1	1.043	0.723～1.503	0.8224
JMDRS (Week 0)			
+10	0.950	0.099～9.105	0.9642
JMDRS (Week 52 or when canceled)			
+10	0.240	0.025～2.309	0.2168

1) Evaluation period of stroke-like episodes before starting the trial
2) 'Stroke-like-episodes' before the start of the trial are defined as 'abrupt-onset focal neurological deficits'.

Program Name: T0701_02_01_b.sas / Output: t0701_02_01_b_f.rtf
Date of Table Generation: 2015-02-17 20:42
Data Source: adatt6

Table 4.2-8 Primary endpoint of the efficacy - 50% responder rate Logistic regression No.1 (PPS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Gender			
Male against Female	0.314	0.007～13.722	0.5481
Age at consent acquisition			
+10 years old	0.796	0.212～2.986	0.7355
Frequency of stroke-like-episodes in the 78 weeks before acquiring consent[1), 2)]			
+1 time	4.117	0.429～39.484	0.2199
Complications			
'None' against 'Present'	5.001	0.178～140.786	0.3446
Smoking history			
'Current smoker' against 'No smoking episode'	N/A	N/A	N/A
'Previous smoker' against 'No smoking episode'	0.520	0.009～29.191	0.7503
Past medical history in the 78 weeks period before acquiring consent[1), 2]			
'None' against 'Present'	1.923	0.034～107.990	0.7503
Blood taurine concentration (Week 0)			
+100nmol/mL	0.368	<0.001～538.335	0.7881
Blood taurine concentration (Week 52 or when canceled)			
+100nmol/mL	1.000	0.669～1.495	1.0000
L-arginine in blood (Week 0)			
+100nmol/mL	0.088	0.006～1.352	0.0812
L-arginine in blood (Week 52 or when canceled)			
+100nmol/mL	1.000	0.204～4.902	1.0000
Lactate in blood (Week 0)			
+10mg/dL	5.490	0.232～129.915	0.2915
Lactate in blood (Week 52 or when canceled)			
+10mg/dL	4.546	0.476～43.434	0.1885

1) Evaluation period of stroke-like episodes before starting the trial
2) 'Stroke-like-episodes' before the start of the trial are defined as 'abrupt-onset focal neurological deficits'.

Program Name: T0701_02_01_b.sas / Output: t0701_02_01_b_p.rtf
Date of Table Generation: 2015-02-17 20:42
Data Source: adatt6

Table 4.2-8 Primary endpoint of the efficacy - 50% responder rate Logistic regression No.1 (PPS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Lactate in CSF (Week 0)			
+10mg/dL	1.032	0.341～3.125	0.9557
Lactate in CSF (Week 52 or when canceled)			
+10mg/dL	1.033	0.400～2.666	0.9468
Pyruvate in blood (Week 0)			
+0.1mg/dL	1.050	0.707～1.559	0.8090
Pyruvate in blood (Week 52 or when canceled)			
+0.1mg/dL	1.337	0.796～2.245	0.2726
Pyruvate in CSF (Week 0)			
+0.1mg/dL	1.017	0.655～1.580	0.9391
Pyruvate in CSF (Week 52 or when canceled)			
+0.1mg/dL	0.985	0.709～1.368	0.9271
Lactate / Pyruvate ratio in blood (Week 0)			
+1	1.152	0.883～1.503	0.2958
Lactate / Pyruvate ratio in blood (Week 52 or when canceled)			
+1	1.125	0.796～1.590	0.5048
Lactate / Pyruvate ratio in CSF (Week 0)			
+1	1.002	0.710～1.414	0.9897
Lactate / Pyruvate ratio in CSF (Week 52 or when canceled)			
+1	1.043	0.723～1.503	0.8224
JMDRS (Week 0)			
+10	0.950	0.099～9.105	0.9642
JM JMDRS (Week 52 or when canceled)			
+10	0.240	0.025～2.309	0.2168

1) Evaluation period of stroke-like episodes before starting the trial
2) 'Stroke-like-episodes' before the start of the trial are defined as 'abrupt-onset focal neurological deficits'.

Program Name: T0701_02_01_b.sas / Output: t0701_02_01_b_p.rtf
Date of Table Generation: 2015-02-17 20:42
Data Source: adatt6

Table 4.2-9 Primary endpoint of the efficacy - 50% responder rate Logistic regression No.2 (FAS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Mitochondrial DNA mutation rate (Week 0)			
+10%	0.969	0.346～2.715	0.9525
Mitochondrial DNA mutation rate (Week 52 or when canceled)			
+10%	1.003	0.370～2.714	0.9958
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 0)			
+0.1folds	1.002	0.965～1.039	0.9286
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 52 or when canceled)			
+0.1folds	0.997	0.986～1.009	0.6389
ND6 protein level (Week 0)			
+10pg/mL	0.039	<0.001～>999.999	0.8375
ND6 protein level (Week 52 or when canceled)			
+10pg/mL	105.682	<0.001～>999.999	0.7967

Program Name: T0701_02_02_b.sas / Output: t0701_02_02_b_f.rtf
Date of Table Generation: 2015-02-17 20:42
Data Source: adattsbl6

Table 4.2-10 Primary endpoint of the efficacy - 50% responder rate Logistic regression No.2 (PPS)

Valuable / unit	Odds ratio		P value
	Point estimate	95% Wald CI	
Mitochondrial DNA mutation rate (Week 0)			
+10%	0.969	0.346～2.715	0.9525
Mitochondrial DNA mutation rate (Week 52 or when canceled)			
+10%	1.003	0.370～2.714	0.9958
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 0)			
+0.1folds	1.002	0.965～1.039	0.9286
$tRNA^{Leu(UUR)}$ taurine modification rate (Week 52 or when canceled)			
+0.1folds	0.997	0.986～1.009	0.6389
ND6 protein level (Week 0)			
+10pg/mL	0.039	<0.001～>999.999	0.8375
ND6 protein level (Week 52 or when canceled)			
+10pg/mL	105.682	<0.001～>999.999	0.7967

Program Name: T0701_02_02_b.sas / Output: t0701_02_02_b_p.rtf
Date of Table Generation: 2015-02-17 20:42
Data Source: adattsbl6

Table 4.2-11 Primary endpoint of the efficacy (FAS)

	Total cases	No L-arginine Co-Administration cases	L-arginine Co-Administration cases
Frequency of the 100% responder			
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 78 weeks period before consent			
N	6	1	5
n (%)	5 (83.3)	1 (100.0)	4 (80.0)
Clopper-Pearson exact 95% confidential interval	35.9, 99.6	2.5, 100.0	28.4, 99.5
Subjects both who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 78 weeks period before acquiring consent and, those who have at least one local neurological sign (confirmed high signal intensity in MRI image of head)			
N	6	1	5
n (%)	6 (100.0)	1 (100.0)	5 (100.0)
Clopper-Pearson exact 95% confidential interval	54.1, 100.0	2.5, 100.0	47.8, 100.0
Subjects who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 78 weeks period before acquiring consent			
N	6	1	5
n (%)	6 (100.0)	1 (100.0)	5 (100.0)
Clopper-Pearson exact 95% confidential interval	54.1, 100.0	2.5, 100.0	47.8, 100.0
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 52 weeks period before acquiring consent			
N	6	1	5
n (%)	2 (33.3)	0 (0.0)	2 (40.0)
Clopper-Pearson exact 95% confidential interval	4.3, 77.7	-, -	5.3, 85.3
Subjects both who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 52 weeks period before acquiring consent			
N	6	1	5
n (%)	6 (100.0)	1 (100.0)	5 (100.0)
Clopper-Pearson exact 95% confidential interval	54.1, 100.0	2.5, 100.0	47.8, 100.0

Program Name: T0701_03.sas / Output: t0701_03_f.rtf
Date of Table Generation: 2015-02-17 20:43
Data Source: adatt6

Table 4.2-11 Primary endpoint of the efficacy (FAS)

	Total cases	No L-arginine Co-Administration cases	L-arginine Co-Administration cases
Frequency of the 100% responder			
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 78 weeks period before consent			
N	8	1	7
n (%)	5 (62.5)	1 (100.0)	4 (57.1)
Clopper-Pearson exact 95% confidential interval	24.5, 91.5	2.5, 100.0	18.4, 90.1
Subjects both who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 78 weeks period before acquiring consent and, those who have at least one local neurological sign (confirmed high signal intensity in MRI image of head)			
N	8	1	7
n (%)	7 (87.5)	1 (100.0)	6 (85.7)
Clopper-Pearson exact 95% confidential interval	47.3, 99.7	2.5, 100.0	42.1, 99.6
Subjects who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 78 weeks period before acquiring consent			
N	8	1	7
n (%)	8 (100.0)	1 (100.0)	7 (100.0)
Clopper-Pearson exact 95% confidential interval	63.1, 100.0	2.5, 100.0	59.0, 100.0
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 52 weeks period before acquiring consent			
N	8	1	7
n (%)	2 (25.0)	0 (0.0)	2 (28.6)
Clopper-Pearson exact 95% confidential interval	3.2, 65.1	-, -	3.7, 71.0
Subjects both who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 52 weeks period before acquiring consent			
N	8	1	7
n (%)	7 (87.5)	1 (100.0)	6 (85.7)
Clopper-Pearson exact 95% confidential interval	47.3, 99.7	2.5, 100.0	42.1, 99.6

Program Name: T0701_03.sas / Output: t0701_03_f.rtf
Date of Table Generation: 2015-02-17 20:43
Data Source: adatt6

Table 4.2-12 Primary endpoint of the efficacy (PPS)

	Total cases	No L-arginine Co-Administration cases	L-arginine Co-Administration cases
Frequency of the 100% responder			
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 78 weeks period before consent			
N	6	1	5
n (%)	5 (83.3)	1 (100.0)	4 (80.0)
Clopper-Pearson exact 95% confidential interval	35.9, 99.6	2.5, 100.0	28.4, 99.5
Subjects both who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 78 weeks period before acquiring consent and, those who have at least one local neurological sign (confirmed high signal intensity in MRI image of head)			
N	6	1	5
n (%)	6 (100.0)	1 (100.0)	5 (100.0)
Clopper-Pearson exact 95% confidential interval	54.1, 100.0	2.5, 100.0	47.8, 100.0
Subjects who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 78 weeks period before acquiring consent			
N	6	1	5
n (%)	6 (100.0)	1 (100.0)	5 (100.0)
Clopper-Pearson exact 95% confidential interval	54.1, 100.0	2.5, 100.0	47.8, 100.0
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 52 weeks period before acquiring consent			
N	6	1	5
n (%)	2 (33.3)	0 (0.0)	2 (40.0)
Clopper-Pearson exact 95% confidential interval	4.3, 77.7	-, -	5.3, 85.3
Subjects both who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 52 weeks period before acquiring consent			
N	6	1	5
n (%)	6 (100.0)	1 (100.0)	5 (100.0)
Clopper-Pearson exact 95% confidential interval	54.1, 100.0	2.5, 100.0	47.8, 100.0

Program Name: T0701_03.sas / Output: t0701_03_p.rtf
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Data Source: adatt6

Table 4.2-12 Primary endpoint of the efficacy (PPS)

	Total cases	No L-arginine Co-Administration cases	L-arginine Co-Administration cases
Frequency of the 100% responder			
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 78 weeks period before consent			
N	8	1	7
n (%)	5 (62.5)	1 (100.0)	4 (57.1)
Clopper-Pearson exact 95% confidential interval	24.5, 91.5	2.5, 100.0	18.4, 90.1
Subjects both who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 78 weeks period before acquiring consent and, those who have at least one local neurological sign (confirmed high signal intensity in MRI image of head)			
N	8	1	7
n (%)	7 (87.5)	1 (100.0)	6 (85.7)
Clopper-Pearson exact 95% confidential interval	47.3, 99.7	2.5, 100.0	42.1, 99.6
Subjects who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 78 weeks period before acquiring consent			
N	8	1	7
n (%)	8 (100.0)	1 (100.0)	7 (100.0)
Clopper-Pearson exact 95% confidential interval	63.1, 100.0	2.5, 100.0	59.0, 100.0
Subjects who have had at least two stroke-like episodes (those that satisfy MELAS Stroke Assessment Criteria) in the 52 weeks period before acquiring consent			
N	8	1	7
n (%)	2 (25.0)	0 (0.0)	2 (28.6)
Clopper-Pearson exact 95% confidential interval	3.2, 65.1	-, -	3.7, 71.0
Subjects both who had at least two abrupt-onset focal neurological deficits (regardless of confirmation of high signal intensity in MRI image of head) in the 52 weeks period before acquiring consent			
N	8	1	7
n (%)	7 (87.5)	1 (100.0)	6 (85.7)
Clopper-Pearson exact 95% confidential interval	47.3, 99.7	2.5, 100.0	42.1, 99.6

Program Name: T0701_03.sas / Output: t0701_03_p.rtf
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Data Source: adatt6

Table 4.2-13 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 1						
Speech: n (%)						
0	2 (20.0)	2 (20.0)	1 (100.0)	1 (100.0)	1 (11.1)	1 (11.1)
1	4 (40.0)	2 (20.0)	0 (0.0)	0 (0.0)	4 (44.4)	2 (22.2)
2	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
3	3 (30.0)	3 (30.0)	0 (0.0)	0 (0.0)	3 (33.3)	3 (33.3)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swallowing: n (%)						
0	9 (90.0)	10 (100.0)	1 (100.0)	1 (100.0)	8 (88.9)	9 (100.0)
1	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Handwriting: n (%)						
0	4 (40.0)	5 (50.0)	1 (100.0)	1 (100.0)	3 (33.3)	4 (44.4)
1	4 (40.0)	3 (30.0)	0 (0.0)	0 (0.0)	4 (44.4)	3 (33.3)
2	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)

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Data Source: adms

Table 4.2-13 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 1						
Cutting food-handling utensils: n (%)						
0	4 (40.0)	5 (50.0)	1 (100.0)	1 (100.0)	3 (33.3)	4 (44.4)
1	6 (60.0)	4 (40.0)	0 (0.0)	0 (0.0)	6 (66.7)	4 (44.4)
2	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dressing: n (%)						
0	5 (50.0)	5 (50.0)	1 (100.0)	1 (100.0)	4 (44.4)	4 (44.4)
1	4 (40.0)	4 (40.0)	0 (0.0)	0 (0.0)	4 (44.4)	4 (44.4)
2	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hygiene: n (%)						
0	5 (50.0)	6 (60.0)	1 (100.0)	1 (100.0)	4 (44.4)	5 (55.6)
1	5 (50.0)	2 (20.0)	0 (0.0)	0 (0.0)	5 (55.6)	2 (22.2)
2	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Data Source: adms

Table 4.2-13 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 1: Activities of daily living						
Falling: n (%)						
0	10 (100.0)	9 (90.0)	1 (100.0)	1 (100.0)	9 (100.0)	8 (88.9)
1	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paroxysmal event (migraine, seizure): n (%)						
0	3 (30.0)	4 (40.0)	0 (0.0)	0 (0.0)	3 (33.3)	4 (44.4)
1	2 (20.0)	3 (30.0)	1 (100.0)	1 (100.0)	1 (11.1)	2 (22.2)
2	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
3	3 (30.0)	2 (20.0)	0 (0.0)	0 (0.0)	3 (33.3)	2 (22.2)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 1						
Mean	5.6	5.6	1.0	1.0	6.1	6.1
SD	3.34	4.06	-	-	3.10	3.95
Median, Minimum, Maximum	5.5, 1, 11	6.0, 1, 12	-, -, -	-, -, -	6.0, 2, 11	7.0, 1, 12

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Data Source: adms

Table 4.2-13 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 2: Motor						
Proximal muscle strength (modified MRC): n (%)						
0	8 (80.0)	7 (70.0)	1 (100.0)	1 (100.0)	7 (77.8)	6 (66.7)
1	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
2	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper limb coordination: n (%)						
0	4 (40.0)	7 (70.0)	1 (100.0)	1 (100.0)	3 (33.3)	6 (66.7)
1	5 (50.0)	2 (20.0)	0 (0.0)	0 (0.0)	5 (55.6)	2 (22.2)
2	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Walking: n (%)						
0	6 (60.0)	4 (40.0)	1 (100.0)	1 (100.0)	5 (55.6)	3 (33.3)
1	3 (30.0)	3 (30.0)	0 (0.0)	0 (0.0)	3 (33.3)	3 (33.3)
2	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Table 4.2-13 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 2						
Moderate motor activities: n (%)						
0	6 (60.0)	5 (50.0)	1 (100.0)	1 (100.0)	5 (55.6)	4 (44.4)
1	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
2	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
3	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vigorous motor activities: n (%)						
0	1 (10.0)	2 (20.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (11.1)
1	2 (20.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (22.2)
2	4 (40.0)	1 (10.0)	0 (0.0)	0 (0.0)	4 (44.4)	1 (11.1)
3	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
4	2 (20.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (22.2)
Total scores of Section 2						
Mean	4.4	4.8	0.0	0.0	4.9	5.3
SD	3.72	4.08	-	-	3.59	3.94
Median, Minimum, Maximum	3.5, 0, 13	4.5, 0, 13	-, -, -	-, -, -	4.0, 1, 13	5.0, 0, 13

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Data Source: adms

Table 4.2-13 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 3: Special sensory						
Vision: (%)						
0	8 (80.0)	7 (70.0)	1 (100.0)	1 (100.0)	7 (77.8)	6 (66.7)
1	2 (20.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (22.2)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Auditory: n (%)						
0	1 (10.0)	2 (20.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (11.1)
1	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)
2	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
3	5 (50.0)	4 (40.0)	0 (0.0)	0 (0.0)	5 (55.6)	4 (44.4)
4	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
Total scores of Section 3						
Mean	2.5	2.9	0.0	0.0	2.8	3.2
SD	1.35	1.85	-	-	1.09	1.64
Median, Minimum, Maximum	3.0, 0, 4	3.0, 0, 7	-, -, -	-, -, -	3.0, 1, 4	3.0, 1, 7

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Data Source: adms

Table 4.2-13 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 4:						
Endocrine disorder: n (%)						
0	7 (70.0)	7 (70.0)	1 (100.0)	1 (100.0)	6 (66.7)	6 (66.7)
1	3 (30.0)	2 (20.0)	0 (0.0)	0 (0.0)	3 (33.3)	2 (22.2)
2	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 4						
Mean	0.3	0.4	0.0	0.0	0.3	0.4
SD	0.48	0.70	-	-	0.50	0.73
Median, Minimum, Maximum	0.0, 0, 1	0.0, 0, 2	-, -, -	-, -, -	0.0, 0, 1	0.0, 0, 2
Section 5						
Cardiac complications: n (%)						
0	5 (50.0)	4 (40.0)	1 (100.0)	1 (100.0)	4 (44.4)	3 (33.3)
1	5 (50.0)	6 (60.0)	0 (0.0)	0 (0.0)	5 (55.6)	6 (66.7)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 5						
Mean	0.5	0.6	0.0	0.0	0.6	0.7
SD	0.53	0.52	-	-	0.53	0.50
Median, Minimum, Maximum	0.5, 0, 1	1.0, 0, 1	-, -, -	-, -, -	1.0, 0, 1	1.0, 0, 1

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Data Source: adms

Table 4.2-13 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)

	Total cases		No L-arginine Co-Administration Cases		L-arginine Co-Administration Cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 6						
Renal function: n (%)						
0	9 (90.0)	9 (90.0)	0 (0.0)	1 (100.0)	9 (100.0)	8 (88.9)
1	1 (10.0)	1 (10.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total score of Section 6						
Mean	0.1	0.1	1.0	0.0	0.0	0.1
SD	0.32	0.32	-	-	0.00	0.33
Median, Minimum, Maximum	0.0, 0, 1	0.0, 0, 1	-, -, -	-, -, -	0.0, 0, 0	0.0, 0, 1
Section 7: Cognitive impairment						
Intellectual impairment: n (%)						
0	2 (20.0)	2 (20.0)	1 (100.0)	1 (100.0)	1 (11.1)	1 (11.1)
1	7 (70.0)	4 (40.0)	0 (0.0)	0 (0.0)	7 (77.8)	4 (44.4)
2	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)
3	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Data Source: adms

Table 4.2-13 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 7						
Motivation and drive: n (%)						
0	5 (50.0)	3 (30.0)	1 (100.0)	1 (100.0)	4 (44.4)	2 (22.2)
1	3 (30.0)	3 (30.0)	0 (0.0)	0 (0.0)	3 (33.3)	3 (33.3)
2	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
3	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 7						
Mean	1.8	2.6	0.0	0.0	2.0	2.9
SD	1.62	2.01	-	-	1.58	1.90
Median, Minimum, Maximum	1.5, 0, 5	2.5, 0, 6	-, -, -	-, -, -	2.0, 0, 5	3.0, 0, 6
Total scores of Section 1-7						
Mean	15.2	17.0	2.0	1.0	16.7	18.8
SD	6.68	9.20	-	-	5.10	7.73
Median, Minimum, Maximum	15.0, 2, 28	18.0, 1, 32	-, -, -	-, -, -	16.0, 11, 28	20.0, 9, 32

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Table 4.2-14 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)
Japanese Mitochondrial Disease Rating Scale (JMDRS) (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 1: Activities of daily living						
Speech: n (%)						
0	2 (20.0)	2 (20.0)	1 (100.0)	1 (100.0)	1 (11.1)	1 (11.1)
1	4 (40.0)	2 (20.0)	0 (0.0)	0 (0.0)	4 (44.4)	2 (22.2)
2	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
3	3 (30.0)	3 (30.0)	0 (0.0)	0 (0.0)	3 (33.3)	3 (33.3)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Swallowing: n (%)						
0	9 (90.0)	10 (100.0)	1 (100.0)	1 (100.0)	8 (88.9)	9 (100.0)
1	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Handwriting: n (%)						
0	4 (40.0)	5 (50.0)	1 (100.0)	1 (100.0)	3 (33.3)	4 (44.4)
1	4 (40.0)	3 (30.0)	0 (0.0)	0 (0.0)	4 (44.4)	3 (33.3)
2	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)

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Table 4.2-14 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)
Japanese Mitochondrial Disease Rating Scale (JMDRS) (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section1:Activities of daily living						
Cutting food-handling utensils: n (%)						
0	4 (40.0)	5 (50.0)	1 (100.0)	1 (100.0)	3 (33.3)	4 (44.4)
1	6 (60.0)	4 (40.0)	0 (0.0)	0 (0.0)	6 (66.7)	4 (44.4)
2	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dressing: n (%)						
0	5 (50.0)	5 (50.0)	1 (100.0)	1 (100.0)	4 (44.4)	4 (44.4)
1	4 (40.0)	4 (40.0)	0 (0.0)	0 (0.0)	4 (44.4)	4 (44.4)
2	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hygiene: n (%)						
0	5 (50.0)	6 (60.0)	1 (100.0)	1 (100.0)	4 (44.4)	5 (55.6)
1	5 (50.0)	2 (20.0)	0 (0.0)	0 (0.0)	5 (55.6)	2 (22.2)
2	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Table 4.2-14 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)
Japanese Mitochondrial Disease Rating Scale (JMDRS) (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 1: Activities of daily living						
Falling: n (%)						
0	10 (100.0)	9 (90.0)	1 (100.0)	1 (100.0)	9 (100.0)	8 (88.9)
1	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Paroxysmal event (migraine, seizure): n (%)						
0	3 (30.0)	4 (40.0)	0 (0.0)	0 (0.0)	3 (33.3)	4 (44.4)
1	2 (20.0)	3 (30.0)	1 (100.0)	1 (100.0)	1 (11.1)	2 (22.2)
2	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
3	3 (30.0)	2 (20.0)	0 (0.0)	0 (0.0)	3 (33.3)	2 (22.2)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 1						
Mean	5.6	5.6	1.0	1.0	6.1	6.1
SD	3.34	4.06	-	-	3.10	3.95
Median, Minimum, Maximum	5.5, 1, 11	6.0, 1, 12	-, -, -	-, -, -	6.0, 2, 11	7.0, 1, 12

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Data Source: adms

Table 4.2-14 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)
Japanese Mitochondrial Disease Rating Scale (JMDRS) (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 2: Motor						
Proximal muscle strength (modified MRC): n (%)						
0	8 (80.0)	7 (70.0)	1 (100.0)	1 (100.0)	7 (77.8)	6 (66.7)
1	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
2	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Upper limb coordination: n (%)						
0	4 (40.0)	7 (70.0)	1 (100.0)	1 (100.0)	3 (33.3)	6 (66.7)
1	5 (50.0)	2 (20.0)	0 (0.0)	0 (0.0)	5 (55.6)	2 (22.2)
2	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Walking: n (%)						
0	6 (60.0)	4 (40.0)	1 (100.0)	1 (100.0)	5 (55.6)	3 (33.3)
1	3 (30.0)	3 (30.0)	0 (0.0)	0 (0.0)	3 (33.3)	3 (33.3)
2	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Table 4.2-14 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)
Japanese Mitochondrial Disease Rating Scale (JMDRS) (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 2: Motor						
Moderate motor activities: n (%)						
0	6 (60.0)	5 (50.0)	1 (100.0)	1 (100.0)	5 (55.6)	4 (44.4)
1	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
2	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
3	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vigorous motor activities: n (%)						
0	1 (10.0)	2 (20.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (11.1)
1	2 (20.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (22.2)
2	4 (40.0)	1 (10.0)	0 (0.0)	0 (0.0)	4 (44.4)	1 (11.1)
3	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
4	2 (20.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (22.2)
Total scores of Section 2						
Mean	4.4	4.8	0.0	0.0	4.9	5.3
SD	3.72	4.08	-	-	3.59	3.94
Median, Minimum, Maximum	3.5, 0, 13	4.5, 0, 13	-, -, -	-, -, -	4.0, 1, 13	5.0, 0, 13

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Table 4.2-14 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)
Japanese Mitochondrial Disease Rating Scale (JMDRS) (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 3: Special sensory						
Vision: n (%)						
0	8 (80.0)	7 (70.0)	1 (100.0)	1 (100.0)	7 (77.8)	6 (66.7)
1	2 (20.0)	2 (20.0)	0 (0.0)	0 (0.0)	2 (22.2)	2 (22.2)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Auditory n (%)						
0	1 (10.0)	2 (20.0)	1 (100.0)	1 (100.0)	0 (0.0)	1 (11.1)
1	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)
2	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
3	5 (50.0)	4 (40.0)	0 (0.0)	0 (0.0)	5 (55.6)	4 (44.4)
4	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
Total scores of Section 3						
Mean	2.5	2.9	0.0	0.0	2.8	3.2
SD	1.35	1.85	-	-	1.09	1.64
Median, Minimum, Maximum	3.0, 0, 4	3.0, 0, 7	-, -, -	-, -, -	3.0, 1, 4	3.0, 1, 7

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Table 4.2-14 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)
Japanese Mitochondrial Disease Rating Scale (JMDRS) (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 4						
Endocrine disorder: n (%)						
0	7 (70.0)	7 (70.0)	1 (100.0)	1 (100.0)	6 (66.7)	6 (66.7)
1	3 (30.0)	2 (20.0)	0 (0.0)	0 (0.0)	3 (33.3)	2 (22.2)
2	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 4						
Mean	0.3	0.4	0.0	0.0	0.3	0.4
SD	0.48	0.70	-	-	0.50	0.73
Median, Minimum, Maximum	0.0, 0, 1	0.0, 0, 2	-, -, -	-, -, -	0.0, 0, 1	0.0, 0, 2
Section 5						
Cardiac complications: n (%)						
0	5 (50.0)	4 (40.0)	1 (100.0)	1 (100.0)	4 (44.4)	3 (33.3)
1	5 (50.0)	6 (60.0)	0 (0.0)	0 (0.0)	5 (55.6)	6 (66.7)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 5						
Mean	0.5	0.6	0.0	0.0	0.6	0.7
SD	0.53	0.52	-	-	0.53	0.50
Median, Minimum, Maximum	0.5, 0, 1	1.0, 0, 1	-, -, -	-, -, -	1.0, 0, 1	1.0, 0, 1

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Table 4.2-14 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)
Japanese Mitochondrial Disease Rating Scale (JMDRS) (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 6						
Renal function: n (%)						
0	9 (90.0)	9 (90.0)	0 (0.0)	1 (100.0)	9 (100.0)	8 (88.9)
1	1 (10.0)	1 (10.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 6						
Mean	0.1	0.1	1.0	0.0	0.0	0.1
SD	0.32	0.32	-	-	0.00	0.33
Median, Minimum, Maximum	0.0, 0, 1	0.0, 0, 1	-, -, -	-, -, -	0.0, 0, 0	0.0, 0, 1
Section 7: Cognitive impairment						
Intellectual impairment: n (%)						
0	2 (20.0)	2 (20.0)	1 (100.0)	1 (100.0)	1 (11.1)	1 (11.1)
1	7 (70.0)	4 (40.0)	0 (0.0)	0 (0.0)	7 (77.8)	4 (44.4)
2	0 (0.0)	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)
3	1 (10.0)	2 (20.0)	0 (0.0)	0 (0.0)	1 (11.1)	2 (22.2)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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Table 4.2-14 Secondary endpoint of the efficacy (1)
Presence or absence of clinical symptoms: Japanese Mitochondrial Disease Rating Scale (JMDRS) (FAS)
Japanese Mitochondrial Disease Rating Scale (JMDRS) (PPS)

	Total cases		No L-arginine Co-Administration Cases		L-arginine Co-Administration cases	
	0 wks N = 10	52 wks (or when canceled) N = 10	0 wks N = 1	52 wks (or when canceled) N = 1	0 wks N = 9	52 wks (or when canceled) N = 9
Section 7						
Motivation and drive: n (%)						
0	5 (50.0)	3 (30.0)	1 (100.0)	1 (100.0)	4 (44.4)	2 (22.2)
1	3 (30.0)	3 (30.0)	0 (0.0)	0 (0.0)	3 (33.3)	3 (33.3)
2	1 (10.0)	3 (30.0)	0 (0.0)	0 (0.0)	1 (11.1)	3 (33.3)
3	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total scores of Section 7						
Mean	1.8	2.6	0.0	0.0	2.0	2.9
SD	1.62	2.01	-	-	1.58	1.90
Median, Minimum, Maximum	1.5, 0, 5	2.5, 0, 6	-, -, -	-, -, -	2.0, 0, 5	3.0, 0, 6
Total scores of Section 1-7						
Mean	15.2	17.0	2.0	1.0	16.7	18.8
SD	6.68	9.20	-	-	5.10	7.73
Median, Minimum, Maximum	15.0, 2, 28	18.0, 1, 32	-, -, -	-, -, -	16.0, 11, 28	20.0, 9, 32

Program Name: T0702_01.sas / Output: t0702_01_p.rtf
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Data Source: adms

Table 4.2-15 Secondary endpoint of the efficacy (2)
50% responder rate (FAS)

	Total cases N = 10	No L-arginine Co-Administration cases N = 1	L-arginine Co-Administration cases N = 9
n (%)	8 (80.0)	1 (100.0)	7 (77.8)
Clopper-Pearson Exact 95% Confidential interval: CI	44.4, 97.5	2.5, 100.0	40.0, 97.2

Program Name: T0702_02.sas / Output: t0702_02_f.rtf
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Data Source: adatt6

Table 4.2-16 Secondary endpoint of the efficacy (2)
50% responder rate (PPS)

	Total cases N = 10	No L-arginine Co-Administration cases N = 1	L-arginine Co-Administration cases N = 9
n (%)	8 (80.0)	1 (100.0)	7 (77.8)
Clopper-Pearson Exact 95% Confidential interval: CI	44.4, 97.5	2.5, 100.0	40.0, 97.2

Program Name: T0702_02.sas / Output: t0702_02_p.rtf
Date of Table Generation: 2015-02-18 17:18
Data Source: adatt6

Table 4.2-17 Secondary endpoint of the efficacy (3)
Number of abrupt-onset focal neurological deficits defined by the MELAS stroke diagnostic criteria with no consideration of confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
	N = 10	N = 10	N = 1	N = 1	N = 9	N = 9
Episodes: n (%)						
0 times	0 (0.0)	4 (40.0)	0 (0.0)	1 (100.0)	0 (0.0)	3 (33.3)
1 times	0 (0.0)	6 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
2 times	4 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (44.4)	0 (0.0)
3 times	2 (20.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (11.1)	0 (0.0)
4 times	4 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (44.4)	0 (0.0)
Frequency of Episodes per month						
Mean	0.170	0.055	0.154	0.000	0.172	0.061
SD	0.0561	0.0475	-	-	0.0591	0.0460
Median, Minimum, Maximum	0.164, 0.10, 0.28	0.090, 0.00, 0.10	-, -, -	-, -, -	0.173, 0.10, 0.28	0.090, 0.00, 0.10

Program Name: T0702_03.sas / Output: t0702_03_f.rtf
Date of Table Generation: 2015-02-18 17:18
Data Source: adatt5

Table 4.2-18 Secondary endpoint of the efficacy (3)
Number of abrupt-onset focal neurological deficits defined by the MELAS stroke diagnostic criteria with no consideration of confirmation of high-intensity lesion(s) with diffusion-weighted brain MRI (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
	N = 10	N = 10	N = 1	N = 1	N = 9	N = 9
Episodes: n (%)						
0 times	0 (0.0)	4 (40.0)	0 (0.0)	1 (100.0)	0 (0.0)	3 (33.3)
1 times	0 (0.0)	6 (60.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (66.7)
2 times	4 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (44.4)	0 (0.0)
3 times	2 (20.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (11.1)	0 (0.0)
4 times	4 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (44.4)	0 (0.0)
Frequency of Episodes per month						
Mean	0.170	0.055	0.154	0.000	0.172	0.061
SD	0.0561	0.0475	-	-	0.0591	0.0460
Median, Minimum, maximum	0.164, 0.10, 0.28	0.090, 0.00, 0.10	-, -, -	-, -, -	0.173, 0.10, 0.28	0.090, 0.00, 0.10

Program Name: T0702_03.sas / Output: t0702_03_p.rtf
Date of Table Generation: 2015-02-18 17:18
Data Source: adatt5

Table 4.2-19 Secondary endpoint of the efficacy (4)
Special examination (FAS)

	Total cases			No L-arginine Co-Administration cases			L-arginine Co-Administration cases		
	0 wks N=10	52 wks (or when canceled) N=10	From 0 wks rate of change N=10	0 wks N=1	52 wks (or when canceled) N=1	From 0 wks rate of change N=1	0 wks N=9	52 wks (or when canceled) N=9	From 0 wks rate of change N=9
Lactic acid in blood (mg/dL)									
n	10	10	10	1	1	1	9	9	9
Mean	32.5	35.8	13.60	25.2	23.8	-5.56	33.3	37.1	15.73
SD	12.97	12.64	30.857	-	-	-	13.48	12.64	31.941
Median	27.0	35.1	8.73	-	-	-	27.5	40.1	9.09
Minimum, Maximum	18, 64	17, 55	-35.1, 70.8	-, -	-, -	-, -	18, 64	17, 55	-35.1, 70.8
Lactic acid in CSF (mg/dL)									
n	7	7	7	1	1	1	6	6	6
Mean	40.5	45.7	22.56	23.6	17.0	-27.97	43.4	50.5	30.98
SD	15.31	17.87	66.000	-	-	-	14.64	13.81	68.055
Median	46.2	46.5	-3.94	-	-	-	49.1	50.1	6.23
Minimum, Maximum	24, 56	17, 67	-28.0, 159.1	-, -	-, -	-, -	24, 56	34, 67	-25.5, 159.1
Pyruvic acid in blood (mg/dL)									
n	10	10	10	1	1	1	9	9	9
Mean	1.3	1.4	19.15	1.5	1.3	-14.97	1.2	1.4	22.94
SD	0.39	0.51	48.942	-	-	-	0.41	0.53	50.330
Median	1.2	1.2	5.81	-	-	-	1.2	1.2	11.63
Minimum, Maximum	1, 2	1, 2	-37.4, 124.2	-, -	-, -	-, -	1, 2	1, 2	-37.4, 124.2

Program Name: T0702_04.sas / Output: t0702_04_f.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: adsmit

Table 4.2-19 Secondary endpoint of the efficacy (4)
Special examination (FAS)

	Total cases			No L-arginine Co-Administration cases			L-arginine Co-Administration cases		
	0 wks N=10	52 wks (or when canceled) N=10	From 0 wks rate of change N=10	0 wks N=1	52 wks (or when canceled) N=1	From 0 wks rate of change N=1	0 wks N=9	52 wks (or when canceled) N=9	From 0 wks rate of change N=9
Pyruvic acid in CSF (mg/dL)									
n	7	7	7	1	1	1	6	6	6
Mean	1.4	1.7	29.78	1.0	0.8	-18.81	1.5	1.9	37.88
SD	0.39	0.52	55.475	-	-	-	0.38	0.37	56.053
Median	1.4	1.7	11.63	-	-	-	1.6	1.8	14.42
Minimum, Maximum	1, 2	1, 2	-18.8, 142.4	-, -	-, -	-, -	1, 2	1, 2	-5.2, 142.4
Ratio of lactic acid / pyruvic acid in blood									
n	10	10	10	1	1	1	9	9	9
Mean	26.14	25.51	0.80	17.14	19.04	11.07	27.14	26.23	-0.34
SD	5.915	4.891	22.899	-	-	-	5.303	4.592	23.985
Median	27.87	24.73	-1.40	-	-	-	29.41	24.93	-2.27
Minimum, Maximum	16.3, 32.0	19.0, 34.0	-23.8, 47.1	-, -	-, -	-, -	16.3, 32.0	19.8, 34.0	-23.8, 47.1
Ratio of lactic acid / pyruvic acid in CSF									
n	7	7	7	1	1	1	6	6	6
Mean	28.47	26.03	-8.31	23.37	20.73	-11.28	29.32	26.92	-7.82
SD	4.934	4.678	9.324	-	-	-	4.810	4.438	10.114
Median	26.55	27.75	-11.28	-	-	-	28.36	27.83	-8.85
Minimum, Maximum	23.4, 36.9	20.7, 32.5	-21.5, 6.9	-, -	-, -	-, -	23.9, 36.9	20.8, 32.5	-21.5, 6.9

Program Name: T0702_04.sas / Output: t0702_04_f.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: adsmit

Table 4.2-19 Secondary endpoint of the efficacy (4)
Special examination (FAS)

	Total cases			No L-arginine Co-Administration cases			L-arginine Co-Administration cases		
	0 wks N=10	52 wks (or when canceled) N=10	From 0 wks rate of change N=10	0 wks N=1	52 wks (or when canceled) N=1	From 0 wks rate of change N=1	0 wks N=9	52 wks (or when canceled) N=9	From 0 wks rate of change N=9
Blood taurine concentration (nmol/mL)									
n	10	10	10	1	1	1	9	9	9
Mean	57.6	945.7	1786.12	57.4	1168.5	1935.71	57.6	920.9	1769.50
SD	20.29	406.18	1288.851	-	-	-	21.53	422.73	1365.895
Median	57.7	1071.8	1376.78	-	-	-	57.9	1028.1	1216.46
Minimum, Maximum	29, 102	189, 1579	226.3, 4359.6	-, -	-, -	-, -	29, 102	189, 1579	226.3, 4359.6
CSF taurine concentration (nmol/mL)									
n	7	7	7	1	1	1	6	6	6
Mean	11.2	42.1	283.26	9.1	30.5	235.16	11.6	44.1	291.27
SD	2.88	13.77	134.531	-	-	-	2.99	14.01	145.529
Median	9.8	39.6	235.44	-	-	-	11.1	42.9	242.21
Minimum, Maximum	8, 16	27, 66	191.8, 583.5	-, -	-, -	-, -	8, 16	27, 66	191.8, 583.5

Program Name: T0702_04.sas / Output: t0702_04_f.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: adsmit

Table 4.2-20 Secondary endpoint of the efficacy (4)
Special examination (PPS)

	Total cases			No L-arginine Co-Administration cases			L-arginine Co-Administration cases		
	0 wks N=10	52 wks (or when canceled) N=10	From 0 wks rate of change N=10	0 wks N=1	52 wks (or when canceled) N=1	From 0 wks rate of change N=1	0 wks N=9	52 wks (or when canceled) N=9	From 0 wks rate of change N=9
Lactic acid in blood (mg/dL)									
n	10	10	10	1	1	1	9	9	9
Mean	32.5	35.8	13.60	25.2	23.8	-5.56	33.3	37.1	15.73
SD	12.97	12.64	30.857	-	-	-	13.48	12.64	31.941
Median	27.0	35.1	8.73	-	-	-	27.5	40.1	9.09
Minimum, Maximum	18, 64	17, 55	-35.1, 70.8	-, -	-, -	-, -	18, 64	17, 55	-35.1, 70.8
Lactic acid in CSF (mg/dL)									
n	7	7	7	1	1	1	6	6	6
Mean	40.5	45.7	22.56	23.6	17.0	-27.97	43.4	50.5	30.98
SD	15.31	17.87	66.000	-	-	-	14.64	13.81	68.055
Median	46.2	46.5	-3.94	-	-	-	49.1	50.1	6.23
Minimum, Maximum	24, 56	17, 67	-28.0, 159.1	-, -	-, -	-, -	24, 56	34, 67	-25.5, 159.1
Pyruvic acid in blood (mg/dL)									
n	10	10	10	1	1	1	9	9	9
Mean	1.3	1.4	19.15	1.5	1.3	-14.97	1.2	1.4	22.94
SD	0.39	0.51	48.942	-	-	-	0.41	0.53	50.330
Median	1.2	1.2	5.81	-	-	-	1.2	1.2	11.63
Minimum, Maximum	1, 2	1, 2	-37.4, 124.2	-, -	-, -	-, -	1, 2	1, 2	-37.4, 124.2

Program Name: T0702_04.sas / Output: t0702_04_p.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: adsmit

Table 4.2-20 Secondary endpoint of the efficacy (4)
Special examination (PPS)

	Total cases			No L-arginine Co-Administration cases			L-arginine Co-Administration cases		
	0 wks N=10	52 wks (or when canceled) N=10	rom 0 wks rate of change N=10	0 wks N=1	52 wks (or when canceled) N=1	From 0 wks rate of change N=1	0 wks N=9	52 wks (or when canceled) N=9	From 0 wks rate of change N=9
Pyruvic acid in CSF (mg/dL)									
n	7	7	7	1	1	1	6	6	6
Mean	1.4	1.7	29.78	1.0	0.8	-18.81	1.5	1.9	37.88
SD	0.39	0.52	55.475	-	-	-	0.38	0.37	56.053
Median	1.4	1.7	11.63	-	-	-	1.6	1.8	14.42
Minimum, Maximum	1, 2	1, 2	-18.8, 142.4	-, -	-, -	-, -	1, 2	1, 2	-5.2, 142.4
Ratio of lactic acid / pyruvic acid in blood									
n	10	10	10	1	1	1	9	9	9
Mean	26.14	25.51	0.80	17.14	19.04	11.07	27.14	26.23	-0.34
SD	5.915	4.891	22.899	-	-	-	5.303	4.592	23.985
Median	27.87	24.73	-1.40	-	-	-	29.41	24.93	-2.27
Minimum, Maximum	16.3, 32.0	19.0, 34.0	-23.8, 47.1	-, -	-, -	-, -	16.3, 32.0	19.8, 34.0	-23.8, 47.1
Ratio of lactic acid / pyruvic acid in CSF									
n	7	7	7	1	1	1	6	6	6
Mean	28.47	26.03	-8.31	23.37	20.73	-11.28	29.32	26.92	-7.82
SD	4.934	4.678	9.324	-	-	-	4.810	4.438	10.114
Median	26.55	27.75	-11.28	-	-	-	28.36	27.83	-8.85
Minimum, Maximum	23.4, 36.9	20.7, 32.5	-21.5, 6.9	-, -	-, -	-, -	23.9, 36.9	20.8, 32.5	-21.5, 6.9

Program Name: T0702_04.sas / Output: t0702_04_p.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: adsmit

Table 4.2-20 Secondary endpoint of the efficacy (4)
Special examination (PPS)

	Total cases			No L-arginine Co-Administration cases			L-arginine Co-Administration cases		
	0 wks N=10	52 wks (or when canceled) N=10	From 0 wks rate of change N=10	0 wks N=1	52 wks (or when canceled) N=1	From 0 wks rate of change N=1	0 wks N=9	52 wks (or when canceled) N=9	From 0 wks rate of change N=9
Blood taurine concentration (nmol/mL)									
n	10	10	10	1	1	1	9	9	9
Mean	57.6	945.7	1786.12	57.4	1168.5	1935.71	57.6	920.9	1769.50
SD	20.29	406.18	1288.851	-	-	-	21.53	422.73	1365.895
Median	57.7	1071.8	1376.78	-	-	-	57.9	1028.1	1216.46
Minimum, Maximum	29, 102	189, 1579	226.3, 4359.6	-, -	-, -	-, -	29, 102	189, 1579	226.3, 4359.6
CSF taurine concentration (nmol/mL)									
n	7	7	7	1	1	1	6	6	6
Mean	11.2	42.1	283.26	9.1	30.5	235.16	11.6	44.1	291.27
SD	2.88	13.77	134.531	-	-	-	2.99	14.01	145.529
Median	9.8	39.6	235.44	-	-	-	11.1	42.9	242.21
Minimum, Maximum	8, 16	27, 66	191.8, 583.5	-, -	-, -	-, -	8, 16	27, 66	191.8, 583.5

Program Name: T0702_04.sas / Output: t0702_04_p.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: adsmit

Table 4.2-21 Secondary endpoint of the efficacy (5)
Shift of the diffusion-weighted images (axial) on the brain MRI (FAS)

		52 wks (or when canceled)				
	-1 wks	Normal	Abnormal (Hyperintense lesion)	Abnormal (Others)	Not examined	Total
Diffusion-weighted images (axial)						
Total cases (N=10)						
Normal	8 (80.0)	6 (100.0)	2 (50.0)	0 (0.0)	0 (0.0)	8 (80.0)
Abnormal (Hyperintense lesion)	2 (20.0)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	2 (20.0)
Abnormal (Others)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	6 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)						
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal (Hyperintense lesion)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal (Others)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)						
Normal	7 (77.8)	5 (100.0)	2 (50.0)	0 (0.0)	0 (0.0)	7 (77.8)
Abnormal (Hyperintense lesion)	2 (22.2)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	2 (22.2)
Abnormal (Others)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	5 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	9 (100.0)

Program Name: T0702_05_a.sas / Output: t0702_05_a_f.rtf
Date of Table Generation: 2015-02-18 21:11
Data Source: admridwi

Table 4.2-22 Secondary endpoint of the efficacy (5)
Shift of the diffusion-weighted images (axial) on the brain MRI (PPS)

		52 wks (or when canceled)				
	-1 wks	Normal	Abnormal (Hyperintense lesion)	Abnormal (Others)	Not examined	Total
Diffusion-weighted images (axial)						
Total cases (N=10)						
Normal	8 (80.0)	6 (100.0)	2 (50.0)	0 (0.0)	0 (0.0)	8 (80.0)
Abnormal (Hyperintense lesion)	2 (20.0)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	2 (20.0)
Abnormal (Others)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	6 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)						
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal (Hyperintense lesion)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal (Others)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)						
Normal	7 (77.8)	5 (100.0)	2 (50.0)	0 (0.0)	0 (0.0)	7 (77.8)
Abnormal (Hyperintense lesion)	2 (22.2)	0 (0.0)	2 (50.0)	0 (0.0)	0 (0.0)	2 (22.2)
Abnormal (Others)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	5 (100.0)	4 (100.0)	0 (0.0)	0 (0.0)	9 (100.0)

Program Name: T0702_05_a.sas / Output: t0702_05_a_p.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admridwi

Table 4.2-23 Secondary endpoint of the efficacy (5)
Shift other than the diffusion-weighted images on the brain MRI (FAS)

		52 wks (or when canceled)			
	-1 wks	Normal	Abnormal	Not examined	Total
MRA (intracranial)					
Total cases (N=10)					
Normal	10 (100.0)	10 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	10 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	9 (100.0)	9 (100.0)	0 (0.0)	0 (0.0)	9 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	9 (100.0)	0 (0.0)	0 (0.0)	9 (100.0)
FLAIR methods (axial)					
Total cases (N=10)					
Normal	2 (20.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (20.0)
Abnormal	8 (80.0)	0 (0.0)	8 (100.0)	0 (0.0)	8 (80.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	2 (100.0)	8 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	1 (11.1)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)
Abnormal	8 (88.9)	0 (0.0)	8 (100.0)	0 (0.0)	8 (88.9)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	1 (100.0)	8 (100.0)	0 (0.0)	9 (100.0)

Program Name: T0702_05_b.sas / Output: t0702_05_b_f.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admrindwi

Table 4.2-23 Secondary endpoint of the efficacy (5)
Shift other than the diffusion-weighted images on the brain MRI (FAS)

		52 wks (or when canceled)			
	-1 wks	Normal	Abnormal	Not examined	Total
T2-weighted images (axial)					
Total cases (N=10)					
Normal	2 (20.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (20.0)
Abnormal	8 (80.0)	0 (0.0)	8 (100.0)	0 (0.0)	8 (80.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	2 (100.0)	8 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	1 (11.1)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)
Abnormal	8 (88.9)	0 (0.0)	8 (100.0)	0 (0.0)	8 (88.9)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	1 (100.0)	8 (100.0)	0 (0.0)	9 (100.0)
T1-weighted images (axial)					
Total cases (N=10)					
Normal	5 (50.0)	2 (100.0)	3 (37.5)	0 (0.0)	5 (50.0)
Abnormal	5 (50.0)	0 (0.0)	5 (62.5)	0 (0.0)	5 (50.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	2 (100.0)	8 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	4 (44.4)	1 (100.0)	3 (37.5)	0 (0.0)	4 (44.4)
Abnormal	5 (55.6)	0 (0.0)	5 (62.5)	0 (0.0)	5 (55.6)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	1 (100.0)	8 (100.0)	0 (0.0)	9 (100.0)

Program Name: T0702_05_b.sas / Output: t0702_05_b_f.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admrindwi

Table 4.2-23 Secondary endpoint of the efficacy (5)
Shift other than the diffusion-weighted images on the brain MRI (FAS)

		52 wks (or when canceled)			
	-1 wks	Normal	Abnormal	Not examined	Total
T2*-weighted images (axial)					
Total cases (N=10)					
Normal	8 (80.0)	8 (100.0)	0 (0.0)	0 (0.0)	8 (80.0)
Abnormal	2 (20.0)	0 (0.0)	2 (100.0)	0 (0.0)	2 (20.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	8 (100.0)	2 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	7 (77.8)	7 (100.0)	0 (0.0)	0 (0.0)	7 (77.8)
Abnormal	2 (22.2)	0 (0.0)	2 (100.0)	0 (0.0)	2 (22.2)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	7 (100.0)	2 (100.0)	0 (0.0)	9 (100.0)
ADC map (axial)					
Total cases (N=10)					
Normal	7 (70.0)	6 (85.7)	1 (33.3)	0 (0.0)	7 (70.0)
Abnormal	3 (30.0)	1 (14.3)	2 (66.7)	0 (0.0)	3 (30.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	7 (100.0)	3 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	6 (66.7)	5 (83.3)	1 (33.3)	0 (0.0)	6 (66.7)
Abnormal	3 (33.3)	1 (16.7)	2 (66.7)	0 (0.0)	3 (33.3)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	6 (100.0)	3 (100.0)	0 (0.0)	9 (100.0)

Program Name: T0702_05_b.sas / Output: t0702_05_b_f.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admrindwi

Table 4.2-24 Secondary endpoint of the efficacy (5)
Shift other than the diffusion-weighted images on the brain MRI (PPS)

		52 wks (or when canceled)			
	-1 wks	Normal	Abnormal	Not examined	Total
MRA (intracranial)					
Total cases (N=10)					
Normal	10 (100.0)	10 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	10 (100.0)	0 (0.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	9 (100.0)	9 (100.0)	0 (0.0)	0 (0.0)	9 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	9 (100.0)	0 (0.0)	0 (0.0)	9 (100.0)
FLAIR methods (axial)					
Total cases (N=10)					
Normal	2 (20.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (20.0)
Abnormal	8 (80.0)	0 (0.0)	8 (100.0)	0 (0.0)	8 (80.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	2 (100.0)	8 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	1 (11.1)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)
Abnormal	8 (88.9)	0 (0.0)	8 (100.0)	0 (0.0)	8 (88.9)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	1 (100.0)	8 (100.0)	0 (0.0)	9 (100.0)

Program Name: T0702_05_b.sas / Output: t0702_05_b_p.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admrindwi

Table 4.2-24 Secondary endpoint of the efficacy (5)
Shift other than the diffusion-weighted images on the brain MRI (PPS)

		52 wks (or when canceled)			
	-1 wks	Normal	Abnormal	Not examined	Total
T2-weighted images (axial)					
Total cases (N=10)					
Normal	2 (20.0)	2 (100.0)	0 (0.0)	0 (0.0)	2 (20.0)
Abnormal	8 (80.0)	0 (0.0)	8 (100.0)	0 (0.0)	8 (80.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	2 (100.0)	8 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	1 (11.1)	1 (100.0)	0 (0.0)	0 (0.0)	1 (11.1)
Abnormal	8 (88.9)	0 (0.0)	8 (100.0)	0 (0.0)	8 (88.9)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	1 (100.0)	8 (100.0)	0 (0.0)	9 (100.0)
T1-weighted images (axial)					
Total cases (N=10)					
Normal	5 (50.0)	2 (100.0)	3 (37.5)	0 (0.0)	5 (50.0)
Abnormal	5 (50.0)	0 (0.0)	5 (62.5)	0 (0.0)	5 (50.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	2 (100.0)	8 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	4 (44.4)	1 (100.0)	3 (37.5)	0 (0.0)	4 (44.4)
Abnormal	5 (55.6)	0 (0.0)	5 (62.5)	0 (0.0)	5 (55.6)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	1 (100.0)	8 (100.0)	0 (0.0)	9 (100.0)

Program Name: T0702_05_b.sas / Output: t0702_05_b_p.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admrindwi

Table 4.2-24 Secondary endpoint of the efficacy (5)
Shift other than the diffusion-weighted images on the brain MRI (PPS)

		52 wks (or when canceled)			
	-1 wks	Normal	Abnormal	Not examined	Total
T2*-weighted images (axial)					
Total cases (N=10)					
Normal	8 (80.0)	8 (100.0)	0 (0.0)	0 (0.0)	8 (80.0)
Abnormal	2 (20.0)	0 (0.0)	2 (100.0)	0 (0.0)	2 (20.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	8 (100.0)	2 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	7 (77.8)	7 (100.0)	0 (0.0)	0 (0.0)	7 (77.8)
Abnormal	2 (22.2)	0 (0.0)	2 (100.0)	0 (0.0)	2 (22.2)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	7 (100.0)	2 (100.0)	0 (0.0)	9 (100.0)
ADC map (axial)					
Total cases (N=10)					
Normal	7 (70.0)	6 (85.7)	1 (33.3)	0 (0.0)	7 (70.0)
Abnormal	3 (30.0)	1 (14.3)	2 (66.7)	0 (0.0)	3 (30.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100.0)	7 (100.0)	3 (100.0)	0 (0.0)	10 (100.0)
No L-arginine Co-Administration case (N=1)					
Normal	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
Abnormal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)
L-arginine Co-Administration cases (N=9)					
Normal	6 (66.7)	5 (83.3)	1 (33.3)	0 (0.0)	6 (66.7)
Abnormal	3 (33.3)	1 (16.7)	2 (66.7)	0 (0.0)	3 (33.3)
Not examined	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	9 (100.0)	6 (100.0)	3 (100.0)	0 (0.0)	9 (100.0)

Program Name: T0702_05_b.sas / Output: t0702_05_b_p.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admrindwi

Table 4.2-25 Secondary endpoint of the efficacy (6)
Frequency of intravenous formulation with L-arginine during pretrial and trial periods: Stroke-like episodes, confirmed by abnormal signal intensity on MRI (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
Number of the administration frequencies of intravenous L-arginine per one-stroke-like episodes: n (%)						
Number of cases	10	10	1	1	9	9
0 times	2 (20.0)	7 (70.0)	1 (100.0)	1 (100.0)	1 (11.1)	6 (66.7)
1 times	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
2 times	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
5 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
6 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
7 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
8 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
36 times	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)

1) "Before administration" is the evaluation period of the stroke-like episodes before the start of the trial, "after administration" is the evaluation period of the stroke-like episodes after the start of the trial.
2) Total number of times intravenous preparation was used for "abrupt-onset of focal neurological deficits" with or without high signal confirmation by MRI.
3) The expression within 2 weeks was counted as "one time" for " abrupt-onset of focal neurological deficits" with or without confirmation of high signal by MRI.
4) Total number of uses of L-arginine intravenous preparation for one stroke-like episode.

Program Name: T0702_06_a.sas / Output: t0702_06_a_f.rtf
Date of Table Generation: 2015-02-18 17:18
Data Source: adatt5, adattnrv

Table 4.2-25 Secondary endpoint of the efficacy (6)
Frequency of intravenous formulation with L-arginine during pretrial and trial periods: Stroke-like episodes, confirmed by abnormal signal intensity on MRI (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
Number of the administration frequencies of intravenous L-arginine per one-stroke-like episodes: n (%)						
Total stroke-like episodes	30	6	3	0	27	6
0 times	12 (40.0)	3 (50.0)	3 (100.0)	0 (0.0)	9 (33.3)	3 (50.0)
1 times	5 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	5 (18.5)	1 (16.7)
2 times	4 (13.3)	1 (16.7)	0 (0.0)	0 (0.0)	4 (14.8)	1 (16.7)
3 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
5 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
7 times	1 (3.3)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.7)	1 (16.7)
8 times	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.1)	0 (0.0)
9 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
10 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
11 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
12 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
13 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
14 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)

Program Name: T0702_06_a.sas / Output: t0702_06_a_f.rtf
Date of Table Generation: 2015-02-18 17:18
Data Source: adatt5, adattnrv

Table 4.2-26 Secondary endpoint of the efficacy (6)
Frequency of intravenous formulation with L-arginine during pretrial and trial periods: Stroke-like episodes, confirmed by abnormal signal intensity on MRI (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
Number of the administration frequencies of intravenous L-arginine per one-stroke-like episodes: n (%)						
Number of cases	10	10	1	1	9	9
0 times	2 (20.0)	7 (70.0)	1 (100.0)	1 (100.0)	1 (11.1)	6 (66.7)
1 times	1 (10.0)	1 (10.0)	0 (0.0)	0 (0.0)	1 (11.1)	1 (11.1)
2 times	2 (20.0)	1 (10.0)	0 (0.0)	0 (0.0)	2 (22.2)	1 (11.1)
5 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
6 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
7 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
8 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
36 times	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)

1) "Before administration" is the evaluation period of the stroke-like episodes before the start of the trial, "after administration" is the evaluation period of the stroke-like episodes after the start of the trial.
2) Total number of times L-arginine intravenous preparation was used for "abrupt-onset of focal neurological deficits" with or without high signal confirmation by MRI.
3) The expression within 2 weeks was counted as "one time" for " abrupt-onset of focal neurological deficits" with or without confirmation of high signal by MRI.
4) Total number of uses of L-arginine intravenous preparation for one stroke-like episode.

Program Name: T0702_06_a.sas / Output: t0702_06_a_f.rtf
Date of Table Generation: 2015-02-18 17:18
Data Source: adatt5, adattnrv

Table 4.2-26 Secondary endpoint of the efficacy (6)
Frequency of intravenous formulation with L-arginine during pretrial and trial periods: Stroke-like episodes, confirmed by abnormal signal intensity on MRI (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
Number of the administration frequencies of intravenous L-arginine per one-stroke-like episodes: n (%)						
Total stroke-like episodes	30	6	3	0	27	6
0 times	12 (40.0)	3 (50.0)	3 (100.0)	0 (0.0)	9 (33.3)	3 (50.0)
1 times	5 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	5 (18.5)	1 (16.7)
2 times	4 (13.3)	1 (16.7)	0 (0.0)	0 (0.0)	4 (14.8)	1 (16.7)
3 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
5 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
7 times	1 (3.3)	1 (16.7)	0 (0.0)	0 (0.0)	1 (3.7)	1 (16.7)
8 times	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (11.1)	0 (0.0)
9 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
10 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
11 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
12 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
13 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)
14 times	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.7)	0 (0.0)

1) "Before administration" is the evaluation period of the stroke-like episodes before the start of the trial, "after administration" is the evaluation period of the stroke-like episodes after the start of the trial.
2) Total number of times L-arginine intravenous preparation was used for "abrupt-onset of focal neurological deficits" with or without high signal confirmation by MRI.
3) The expression within 2 weeks was counted as "one time" for " abrupt-onset of focal neurological deficits" with or without confirmation of high signal by MRI.
4) Total number of uses of L-arginine intravenous preparation for one stroke-like episode.

Program Name: T0702_06_a.sas / Output: t0702_06_a_f.rtf
Date of Table Generation: 2015-02-18 17:18
Data Source: adatt5, adattnrv

Table 4.2-27 Secondary endpoint of the efficacy (6)
Frequency of intravenous formulation with L-arginine during pretrial and trial periods: Stroke-like episodes, confirmed by abnormal signal intensity on MRI (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
Number of administration[2)] : n (%)						
Number of cases	10	10	1	1	9	9
0 times	5 (50.0)	7 (70.0)	1 (100.0)	1 (100.0)	4 (44.4)	6 (66.7)
1 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
2 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
4 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
5 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
7 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
8 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
35 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
36 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)

1) "Before administration" is the evaluation period of the stroke-like attack before the start of the trial, "after administration" is the evaluation period of the stroke-like attack after the start of the trial
2) In "Before administration", the total number of times the L-arginine intravenous preparation was used for "abrupt-onset focal neurological deficits" regardless of whether or not high signal confirmation by MRI was confirmed
"After administration", the total number of times the L-arginine intravenous preparation was used for the "abrupt-onset focal neurological deficits" confirmed high signal by MRI
3) In "before administration", the expression within 2 weeks was counted as "one time" for "abrupt-onset focal neurological deficits" irrespective of whether high signal was confirmed by MRI
"After administration" counts the expression within 2 weeks as "one time" for "abrupt-onset focal neurological deficits" confirmed high signal by MRI
4) Total number of uses of L-arginine intravenous preparation for one seizure

Program Name: T0702_06_b.sas / Output: t0702_06_b_f.rtf
Date of Table Generation: 2015-02-18 17:19
Data Source: adatt5, adatt4

Table 4.2-27 Secondary endpoint of the efficacy (6)
Frequency of intravenous formulation with L-arginine during pretrial and trial periods: Stroke-like episodes, confirmed by abnormal signal intensity on MRI (FAS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
Number of the administration frequencies of intravenous L-arginine per one-stroke-like episodes[44] : n (%)						
Total stroke-like episodes	17	4	2	0	15	4
0 times	5 (29.4)	1 (25.0)	2 (100.0)	0 (0.0)	3 (20.0)	1 (25.0)
1 times	1 (5.9)	1 (25.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (25.0)
2 times	2 (11.8)	1 (25.0)	0 (0.0)	0 (0.0)	2 (13.3)	1 (25.0)
3 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
5 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
7 times	1 (5.9)	1 (25.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (25.0)
8 times	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (20.0)	0 (0.0)
9 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
10 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
11 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
12 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
13 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
14 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)

1) "Before administration" is the evaluation period of the stroke-like attack before the start of the trial, "after administration" is the evaluation period of the stroke-like attack after the start of the trial
2) In "Before administration", the total number of times the L-arginine intravenous preparation was used for "abrupt-onset focal neurological deficits" regardless of whether or not high signal confirmation by MRI was confirmed
"After administration", the total number of times the L-arginine intravenous preparation was used for the "abrupt-onset focal neurological deficits" confirmed high signal by MRI
3) In "before administration", the expression within 2 weeks was counted as "one time" for "abrupt-onset focal neurological deficits" irrespective of whether high signal was confirmed by MRI
"After administration" counts the expression within 2 weeks as "one time" for "abrupt-onset focal neurological deficits" confirmed high signal by MRI
4) Total number of uses of L-arginine intravenous preparation for one seizure

Program Name: T0702_06_b.sas / Output: t0702_06_b_f.rtf
Date of Table Generation: 2015-02-18 17:19
Data Source: adatt5, adatt4

Table 4.2-28 Secondary endpoint of the efficacy (6)
Frequency of intravenous formulation with L-arginine during pretrial and trial periods: Stroke-like episodes, confirmed by abnormal signal intensity on MRI (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-Administration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
Number of administration[2)] : n (%)						
Number of cases	10	10	1	1	9	9
0 times	5 (50.0)	7 (70.0)	1 (100.0)	1 (100.0)	4 (44.4)	6 (66.7)
1 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
2 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
4 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
5 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
7 times	0 (0.0)	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)
8 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
35 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
36 times	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)

1) "Before administration" is the evaluation period of the stroke-like attack before the start of the trial, "after administration" is the evaluation period of the stroke-like attack after the start of the trial
2) In "Before administration", the total number of times the L-arginine intravenous preparation was used for "abrupt-onset focal neurological deficits" regardless of whether or not high signal confirmation by MRI was confirmed
"After administration", the total number of times the L-arginine intravenous preparation was used for the "abrupt-onset focal neurological deficits" confirmed high signal by MRI
3) In "before administration", the expression within 2 weeks was counted as "one time" for "abrupt-onset focal neurological deficits" irrespective of whether high signal was confirmed by MRI
"After administration" counts the expression within 2 weeks as "one time" for "abrupt-onset focal neurological deficits" confirmed high signal by MRI
4) Total number of uses of L-arginine intravenous preparation for one seizure

Program Name: T0702_06_b.sas / Output: t0702_06_b_p.rtf
Date of Table Generation: 2015-02-18 17:19
Data Source: adatt5, adatt4

Table 4.2-28 Secondary endpoint of the efficacy (6)
Frequency of intravenous formulation with L-arginine during pretrial and trial periods: Stroke-like episodes, confirmed by abnormal signal intensity on MRI (PPS)

	Total cases		No L-arginine Co-Administration cases		L-arginine Co-aAdministration cases	
	Pretrial period	Trial period	Pretrial period	Trial period	Pretrial period	Trial period
Number of the administration frequencies of intravenous L-arginine per one-stroke-like episodes[4)] : n (%)						
Total stroke-like episodes	17	4	2	0	15	4
0 times	5 (29.4)	1 (25.0)	2 (100.0)	0 (0.0)	3 (20.0)	1 (25.0)
1 times	1 (5.9)	1 (25.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (25.0)
2 times	2 (11.8)	1 (25.0)	0 (0.0)	0 (0.0)	2 (13.3)	1 (25.0)
3 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
5 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
6 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
7 times	1 (5.9)	1 (25.0)	0 (0.0)	0 (0.0)	1 (6.7)	1 (25.0)
8 times	3 (17.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (20.0)	0 (0.0)
9 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
10 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
11 times	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
12 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
13 times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)
14 Times	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)	0 (0.0)

1) "Before administration" is the evaluation period of the stroke-like attack before the start of the trial, "after administration" is the evaluation period of the stroke-like attack after the start of the trial
2) In "Before administration", the total number of times the L-arginine intravenous preparation was used for "abrupt-onset focal neurological deficits" regardless of whether or not high signal confirmation by MRI was confirmed
"After administration", the total number of times the L-arginine intravenous preparation was used for the "abrupt-onset focal neurological deficits" confirmed high signal by MRI
3) In "before administration", the expression within 2 weeks was counted as "one time" for "abrupt-onset focal neurological deficits" irrespective of whether high signal was confirmed by MRI
"After administration" counts the expression within 2 weeks as "one time" for "abrupt-onset focal neurological deficits" confirmed high signal by MRI
4) Total number of uses of L-arginine intravenous preparation for one seizure

Program Name: T0702_06_b.sas / Output: t0702_06_b_p.rtf
Date of Table Generation: 2015-02-18 17:19
Data Source: adatt5, adatt4

Table 4.2-29 Secondary endpoint of the efficacy (7)
Number of times high-intensity lesion(s) are confirmed with diffusion-weighted brain MRI in the presence of headache, nausea/vomiting, convulsions, or impaired consciousness [1] (FAS)

	Total cases N = 10	No L-arginine Co-Administration cases N = 1	L-arginine Co-Administration cases N = 9
Number of encounters: n (%)			
0 times	9 (90.0)	1 (100.0)	8 (88.9)
1 times	1 (10.0)	0 (0.0)	1 (11.1)

1) In "the evaluation period of the stroke-like episode after administration", the number of high signal confirmations when head MRIs were performed upon occurrence of headache, nausea and vomiting, convulsions, and disturbed consciousness. The expression within 2 weeks was counted as "one time" for "abrupt-onset focal neurological deficits" onfirmed high signal by MRI.

Program Name: T0702_07.sas / Output: t0702_07_f.rtf
Date of Table Generation: 2015-02-18 17:19
Data Source: adatt5

Table 4.2-30 Secondary endpoint of the efficacy (7)
Number of times high-intensity lesion(s) are confirmed with diffusion-weighted brain MRI in the presence of headache, nausea/vomiting, convulsions, or impaired consciousness [1] (PPS)

	Total cases N = 10	No L-arginine Co-Administration cases N = 1	L-arginine Co-Administration cases N = 9
Number of encounters: n (%)			
0 times	9 (90.0)	1 (100.0)	8 (88.9)
1 times	1 (10.0)	0 (0.0)	1 (11.1)

1) In "the evaluation period of the stroke-like episode after administration", the number of high signal confirmations when head MRIs were performed upon occurrence of headache, nausea and vomiting, convulsions, and disturbed consciousness. The expression within 2 weeks was counted as "one time" for "abrupt-onset focal neurological deficits" confirmed high signal by MRI.

Program Name: T0702_07.sas / Output: t0702_07_p.rtf
Date of Table Generation: 2015-02-18 17:19
Data Source: adatt5

Table 4.2-31 Secondary endpoint of the efficacy: MMSE score (FAS)

	Total cases		No L-arginine-Co-Administration cases		L-arginine-Co-Administration cases	
	0 wks	52 wks (or when canceled)	0 wks	52 wks (or when canceled)	0 wks	52 wks (or when canceled)
	N=10	N=9	N=1	N=1	N=9	N=8
Orientation to time: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
4	1 (10.0)	3 (33.3)	0 (0.0)	0 (0.0)	1 (11.1)	3 (37.5)
5	8 (80.0)	6 (66.7)	1 (100.0)	1 (100.0)	7 (77.8)	5 (62.5)
Orientation to place: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
2	1 (10.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)	1 (12.5)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	4 (40.0)	1 (11.1)	0 (0.0)	0 (0.0)	4 (44.4)	1 (12.5)
5	5 (50.0)	6 (66.7)	1 (100.0)	1 (100.0)	4 (44.4)	5 (62.5)
Registration: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)
3	8 (80.0)	9 (100.0)	1 (100.0)	1 (100.0)	7 (77.8)	8 (100.0)
Attention and calculation: n (%)						
0	2 (20.0)	2 (22.2)	0 (0.0)	0 (0.0)	2 (22.2)	2 (25.0)
1	4 (40.0)	1 (11.1)	1 (100.0)	0 (0.0)	3 (33.3)	1 (12.5)
2	2 (20.0)	3 (33.3)	0 (0.0)	0 (0.0)	2 (22.2)	3 (37.5)
3	1 (10.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)	1 (12.5)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	1 (10.0)	2 (22.2)	0 (0.0)	1 (100.0)	1 (11.1)	1 (12.5)
Recall: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	2 (20.0)	1 (11.1)	1 (100.0)	0 (0.0)	1 (11.1)	1 (12.5)
3	8 (80.0)	8 (88.9)	0 (0.0)	1 (100.0)	8 (88.9)	7 (87.5)
Naming: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	10 (100.0)	9 (100.0)	1 (100.0)	1 (100.0)	9 (100.0)	8 (100.0)

Program Name: T0703.sas / Output: t0703_f.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admmse

Table 4.2-31 Secondary endpoint of the efficacy: MMSE score (FAS)

	Total cases		No L-arginine-Co-Administration cases		L-arginine-Co-Administration cases	
	0 wks	52 wks (or when canceled)	0 wks	52 wks (or when canceled)	0 wks	52 wks (or when canceled)
	N=10	N=9	N=1	N=1	N=9	N=8
Repetition: n (%)						
0	5 (50.0)	3 (33.3)	0 (0.0)	0 (0.0)	5 (55.6)	3 (37.5)
1	5 (50.0)	6 (66.7)	1 (100.0)	1 (100.0)	4 (44.4)	5 (62.5)
Talking instructions: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
3	9 (90.0)	9 (100.0)	1 (100.0)	1 (100.0)	8 (88.9)	8 (100.0)
Write instructions: n (%)						
0	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
1	10 (100.0)	8 (88.9)	1 (100.0)	1 (100.0)	9 (100.0)	7 (87.5)
Spontaneous writing: n (%)						
0	1 (10.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)	1 (12.5)
1	9 (90.0)	8 (88.9)	1 (100.0)	1 (100.0)	8 (88.9)	7 (87.5)
Figure reproduction: n (%)						
0	3 (30.0)	2 (22.2)	0 (0.0)	0 (0.0)	3 (33.3)	2 (25.0)
1	7 (70.0)	7 (77.8)	1 (100.0)	1 (100.0)	6 (66.7)	6 (75.0)
Total scores						
Number of cases	10	9	1	1	9	8
Mean	24.2	25.1	25.0	30.0	24.1	24.5
SD	3.74	4.37	-	-	3.95	4.24
Median, Minimum, Maximum	25.0, 16, 30	27.0, 19, 30	-, -, -	-, -, -	25.0, 16, 30	26.0, 19, 30

Program Name: T0703.sas / Output: t0703_f.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admmse

Table 4.2-32 Secondary endpoint of the efficacy: MMSE score (PPS)

	Total cases		No L-arginine-Co-Administration cases		L-arginine-Co-Administration cases	
	0 wks	52 wks (or when canceled)	0 wks	52 wks (or when canceled)	0 wks	52 wks (or when canceled)
	N=10	N=9	N=1	N=1	N=9	N=8
Orientation to time: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
3	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
4	1 (10.0)	3 (33.3)	0 (0.0)	0 (0.0)	1 (11.1)	3 (37.5)
5	8 (80.0)	6 (66.7)	1 (100.0)	1 (100.0)	7 (77.8)	5 (62.5)
Orientation to place: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
2	1 (10.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)	1 (12.5)
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
4	4 (40.0)	1 (11.1)	0 (0.0)	0 (0.0)	4 (44.4)	1 (12.5)
5	5 (50.0)	6 (66.7)	1 (100.0)	1 (100.0)	4 (44.4)	5 (62.5)
Registration: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	2 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (22.2)	0 (0.0)
3	8 (80.0)	9 (100.0)	1 (100.0)	1 (100.0)	7 (77.8)	8 (100.0)
Attention and calculation: n (%)						
0	2 (20.0)	2 (22.2)	0 (0.0)	0 (0.0)	2 (22.2)	2 (25.0)
1	4 (40.0)	1 (11.1)	1 (100.0)	0 (0.0)	3 (33.3)	1 (12.5)
2	2 (20.0)	3 (33.3)	0 (0.0)	0 (0.0)	2 (22.2)	3 (37.5)
3	1 (10.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)	1 (12.5)
4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
5	1 (10.0)	2 (22.2)	0 (0.0)	1 (100.0)	1 (11.1)	1 (12.5)
Recall: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	2 (20.0)	1 (11.1)	1 (100.0)	0 (0.0)	1 (11.1)	1 (12.5)
3	8 (80.0)	8 (88.9)	0 (0.0)	1 (100.0)	8 (88.9)	7 (87.5)
Naming: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	10 (100.0)	9 (100.0)	1 (100.0)	1 (100.0)	9 (100.0)	8 (100.0)

Program Name: T0703.sas / Output: t0703_p.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admmse

Table 4.2-32 Secondary endpoint of the efficacy: MMSE score (PPS)

	Total cases		No L-arginine-Co-Administration cases		L-arginine-Co-Administration cases	
	0 wks	52 wks (or when canceled)	0 wks	52 wks (or when canceled)	0 wks	52 wks (or when canceled)
	N=10	N=9	N=1	N=1	N=9	N=8
Repetition: n (%)						
0	5 (50.0)	3 (33.3)	0 (0.0)	0 (0.0)	5 (55.6)	3 (37.5)
1	5 (50.0)	6 (66.7)	1 (100.0)	1 (100.0)	4 (44.4)	5 (62.5)
Talking instructions: n (%)						
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	1 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	0 (0.0)
3	9 (90.0)	9 (100.0)	1 (100.0)	1 (100.0)	8 (88.9)	8 (100.0)
Write instructions: n (%)						
0	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)
1	10 (100.0)	8 (88.9)	1 (100.0)	1 (100.0)	9 (100.0)	7 (87.5)
Spontaneous writing: n (%)						
0	1 (10.0)	1 (11.1)	0 (0.0)	0 (0.0)	1 (11.1)	1 (12.5)
1	9 (90.0)	8 (88.9)	1 (100.0)	1 (100.0)	8 (88.9)	7 (87.5)
Figure reproduction: n (%)						
0	3 (30.0)	2 (22.2)	0 (0.0)	0 (0.0)	3 (33.3)	2 (25.0)
1	7 (70.0)	7 (77.8)	1 (100.0)	1 (100.0)	6 (66.7)	6 (75.0)
Total score						
Number of cases	10	9	1	1	9	8
Mean	24.2	25.1	25.0	30.0	24.1	24.5
SD	3.74	4.37	-	-	3.95	4.24
Median, Minimum, Maximum	25.0, 16, 30	27.0, 19, 30	-, -, -	-, -, -	25.0, 16, 30	26.0, 19, 30

Program Name: T0703.sas / Output: t0703_p.rtf
Date of Table Generation: 2015-02-18 21:12
Data Source: admmse

Table 4.3.1-1 Summary of Adverse Events (Safety Analysis)

Item	Total cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Adverse Events	10 (100.0)	1 (100.0)	9 (100.0)
Serious adverse event	2 (20.0)	0 (0.0)	2 (22.2)
Dead case	0 (0.0)	0 (0.0)	0 (0.0)
Adverse events leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
Severity [1)]			
Mild	5 (50.0)	1 (100.0)	4 (44.4)
Moderate	5 (50.0)	0 (0.0)	5 (55.6)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Relationship with taurine [2)]			
No	4 (40.0)	0 (0.0)	4 (44.4)
Yes	6 (60.0)	1 (100.0)	5 (55.6)

1) When multiple adverse events are observed in the same subject, the most severe adverse event is counted.
2) When multiple adverse events are observed in the same subject and their relationship with the investigational product is mixed with "Related" and "Unrelated", the result is counted as "Related."

Program Name: T080101_01.sas / Output: t080101_01.rtf
Date of Table Generation: 2015-02-17 21:03
Data Source: adae

Table 4.3.1-2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Adverse event	-	10 (100.0)	1 (100.0)	9 (100.0)
Blood and lymphatic system disorders		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Leukocytosis		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Ear and labyrinthine disorders		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Otalgia		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Ocular disorder		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Allergic conjunctivitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Gastrointestinal problems		7 (70.0)	1 (100.0)	6 (66.7)
	mild	6 (60.0)	1 (100.0)	5 (55.6)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Diarrhea		4 (40.0)	1 (100.0)	3 (33.3)
	mild	4 (40.0)	1 (100.0)	3 (33.3)
Vomiting		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Stomachache		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

1) MedDRA Ver. 17.1 was used.
2) When multiple adverse events were observed in the same subject in the same SOC and the same PT, the most severe adverse events were counted.

Program Name: T080101_02.sas / Output: t080101_02_a.rtf
Date of Table Generation: 2015-02-17 21:03
Data Source: adae

Table 4.3.1-2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
(Gastrointestinal problems Continued)				
Epigastric pain		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Constipation		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Gastritis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Reflux esophagitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Hiatal hernia		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Stomatitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Toothache		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
General・general disability and state of administration site		3 (30.0)	0 (0.0)	3 (33.3)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Fever		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Fatigue		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Infectious diseases and parasitic diseases		7 (70.0)	0 (0.0)	7 (77.8)
	mild	4 (40.0)	0 (0.0)	4 (44.4)
	moderate	3 (30.0)	0 (0.0)	3 (33.3)

1) MedDRA Ver. 17.1 was used.
2) When multiple adverse events were observed in the same subject in the same SOC and the same PT, the most severe adverse events were counted.

Program Name: T080101_02.sas / Output: t080101_02_a.rtf
Date of Table Generation: 2015-02-17 21:03
Data Source: adae

Table 4.3.1-2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
(Infectious diseases and parasitic diseases Continued)				
Nasopharyngeitis		5 (50.0)	0 (0.0)	5 (55.6)
	mild	3 (30.0)	0 (0.0)	3 (33.3)
	moderate	2 (20.0)	0 (0.0)	2 (22.2)
Influenza		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Gastroenteritis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Viral gastroenteritis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Gingivitis		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Herpes zoster		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Rhinitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Tinea infection		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Injury, poisoning and treatment complications		3 (30.0)	0 (0.0)	3 (33.3)
	mild	3 (30.0)	0 (0.0)	3 (33.3)
Contusion		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Ligament sprain		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Lumbar puncture syndrome		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

1) MedDRA Ver. 17.1 was used.
2) When multiple adverse events were observed in the same subject in the same SOC and the same PT, the most severe adverse events were counted.

Program Name: T080101_02.sas / Output: t080101_02_a.rtf
Date of Table Generation: 2015-02-17 21:03
Data Source: adae

Table 4.3.1-2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
(Injury, poisoning and treatment complications Continued)				
Peel fracture		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Laboratory test		6 (60.0)	0 (0.0)	6 (66.7)
	mild	4 (40.0)	0 (0.0)	4 (44.4)
	moderate	2 (20.0)	0 (0.0)	2 (22.2)
Serum creatine kinase elevation		3 (30.0)	0 (0.0)	3 (33.3)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
C-reactive protein elevation		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Increase of γ-glutamyl transferase		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Increase in neutrophil count		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Alanine aminotransferase increase		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Aspartate aminotransferase increase		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Increase blood lactate dehydrogenase		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Increase in blood potassium		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Blood triglyceride increase		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

1) MedDRA Ver. 17.1 was used.
2) When multiple adverse events were observed in the same subject in the same SOC and the same PT, the most severe adverse events were counted.

Program Name: T080101_02.sas / Output: t080101_02_a.rtf
Date of Table Generation: 2015-02-17 21:03
Data Source: adae

Table 4.3.1-2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
(Laboratory test Continued)				
Heart rate increase		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Lymphocyte count reduction		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Increase in white blood cell count		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Metabolism and malnutrition		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Dehydration		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Appetite loss		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Musculoskeletal system and connective tissue disorder		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Arthralgia		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Arthritis		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Limb pain		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Disorder of nervous system		3 (30.0)	0 (0.0)	3 (33.3)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)

1) MedDRA Ver. 17.1 was used.
2) When multiple adverse events were observed in the same subject in the same SOC and the same PT, the most severe adverse events were counted.

Program Name: T080101_02.sas / Output: t080101_02_a.rtf
Date of Table Generation: 2015-02-17 21:03
Data Source: adae

Table 4.3.1-2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
(Disorder of nervous system Continued)				
Convulsion		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Headache		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Post herpetic neuralgia		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Mental disorder		2 (20.0)	0 (0.0)	2 (22.2)
	mild	2 (20.0)	0 (0.0)	2 (22.2)
Auditory hallucination		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Sleepless		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Renal and urinary tract disorder		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Urinary frequency		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Respiratory, thoracic and mediastinal disorders		2 (20.0)	0 (0.0)	2 (22.2)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Aspiration pneumonia		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Inflammation of upper respiratory tract		1 (10.0)	0 (0.0)	1 (11.1)
	moderate	1 (10.0)	0 (0.0)	1 (11.1)
Skin and subcutaneous tissue injury		3 (30.0)	0 (0.0)	3 (33.3)
	mild	3 (30.0)	0 (0.0)	3 (33.3)

1) MedDRA Ver. 17.1 was used.
2) When multiple adverse events were observed in the same subject in the same SOC and the same PT, the most severe adverse events were counted.

Program Name: T080101_02.sas / Output: t080101_02_a.rtf
Date of Table Generation: 2015-02-17 21:03
Data Source: adae

Table 4.3.1-2 Frequency of adverse events by SOC, PT and severity (safety analysis)

SOC[1)] PT[1)]	Severity[2)]	Total cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
(Skin and subcutaneous tissue injury Continued)				
Keloid scar		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Rash		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Hand dermatitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

1) MedDRA Ver. 17.1 was used.
2) When multiple adverse events were observed in the same subject in the same SOC and the same PT, the most severe adverse events were counted.

Program Name: T080101_02.sas / Output: t080101_02_a.rtf
Date of Table Generation: 2015-02-17 21:03
Data Source: adae

Table 4.3.1-3 Frequency of Side Effects by SOC, PT and Severity (Safety Analysis)

SOC[1)] PT[1)]	Severity[2)]	Total cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Side effect	-	6 (60.0)	1 (100.0)	5 (55.6)
Gastrointestinal disorder		3 (30.0)	1 (100.0)	2 (22.2)
	mild	3 (30.0)	1 (100.0)	2 (22.2)
Constipation		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Diarrhea		1 (10.0)	1 (100.0)	0 (0.0)
	mild	1 (10.0)	1 (100.0)	0 (0.0)
Gastroesophageal reflux disease		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Hiatal hernia		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Stomatitis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Infections and parasitosis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Gastroenteritis		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Laboratory test		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Increase of γ-glutamyl transferase		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Metabolism and nutritional disorders		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Appetite loss		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

1) MedDRA Ver. 17.1 was used.
2) When multiple side effects were observed in the same subject in the same SOC and the same PT, the most severe side effects were counted.

Program Name: T080101_02.sas / Output: t080101_02_b.rtf
Date of Table Generation: 2015-02-17 21:03
Data Source: adae

Table 4.3.1-3 Frequency of Side Effects by SOC, PT and Severity (Safety Analysis)

SOC[1)] PT[1)]	Severity[2)]	Total cases N = 10 n (%)	No L-arginine Co-Administration cases N = 1 n (%)	L-arginine Co-Administration cases N = 9 n (%)
Mental disorder		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Sleepless		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Renal and urinary tract disorder		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)
Urinary frequency		1 (10.0)	0 (0.0)	1 (11.1)
	mild	1 (10.0)	0 (0.0)	1 (11.1)

1) MedDRA Ver. 17.1 was used.
2) When multiple side effects were observed in the same subject in the same SOC and the same PT, the most severe side effects were counted.

Program Name: T080101_02.sas / Output: t080101_02_b.rtf
Date of Table Generation: 2015-02-17 21:03
Data Source: adae

Table 4.3.2-2 Serious Adverse Event List (Safety Analysis)

Subject identification number, without・with the Co-Administration of L-arginine/ Name of adverse event described by doctor (SOC[1)]/PT[1)])	Date of occurrence	Date of resolution	Period of occurrence (day)[2)]	Degree of seriousness	Breakdown of seriousness[3)]	Severity	Treatment	Outcome	Measures for investigational drugs	Relationship with taurine	Comment
KN-03-01, with the co-administration of L-arginine											
Serum CK elevation (Laboratory test/ increase in blood creatine phosphokinase)	2014/04/18	2014/05/20	33	serious	3	moderate	none	Recovery	continued	No	symptoms caused by MELAS
KN-10-01, with the co-administration of L-arginine											
Acute Gastroenteritis (Infectious diseases and parasitic diseases/ Gastroenteritis)	2014/04/10	2014/05/19	40	serious	3	mild	drug treatment	Recovery	continued	No	Infection

1) MedDRA Ver. 17.1 was used
2) Outcome date - Appearance date + 1
3) 1: death, 2: threatened to death, 3: hospital or clinic hospitalization for treatment or extension of hospitalization period (excluding examination hospitalization), 4: Failure, 5: things that may lead to disability, those that are serious according to the cases listed in 6: 1 to 5, 7: congenital diseases or abnormalities in the later generations

Program Name: L080101.sas / Output: l080101_c.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adae

Table 4.3.4-1 Change in laboratory value: Hematological Tests (In-hospital) (Safety Analysis)
Total cases

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks (or when canceled) N = 10
RBC count (10^4/μL)						
n	10	10	10	10	10	10
Mean	442.3	441.0	461.6	455.7	458.7	450.1
SD	24.90	24.72	28.72	34.45	35.16	44.36
Median	448.0	434.5	462.5	451.5	453.0	441.0
Minimum, Maximum	407, 472	407, 491	397, 500	401, 499	412, 514	390, 535
WBC count (/μL)						
n	10	10	10	10	10	10
Mean	5983.0	6106.0	6321.0	6339.0	6393.0	6455.0
SD	1522.63	1331.00	2012.89	1100.11	1244.51	1617.40
Median	6150.0	6460.0	5665.0	6220.0	6050.0	6870.0
Minimum, Maximum	3220, 8250	3400, 7800	3500, 10400	5200, 8300	4990, 8700	3800, 8100
Blood platelet count (10^4/μL)						
n	10	10	10	10	10	10
Mean	25.70	27.60	27.54	27.53	27.87	28.44
SD	7.962	7.955	8.977	7.965	8.621	8.745
Median	21.90	27.15	24.85	26.95	26.35	25.95
Minimum, Maximum	15.7, 38.6	18.5, 38.0	16.8, 43.0	18.6, 39.5	17.1, 41.8	18.6, 43.3

Program Name: T080102.sas / Output: t080102_a.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbhm

Table 4.3.4-1 Change in laboratory value: Hematological Tests (In-hospital) (Safety Analysis)
Total cases

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks (or when canceled) N = 10
Hemoglobin content (g/dL)						
n	10	10	10	10	10	10
Mean	13.37	13.33	13.83	13.39	13.50	13.05
SD	0.914	0.967	1.145	1.297	1.454	1.523
Median	13.60	13.30	14.15	13.40	13.95	13.50
Minimum, Maximum	12.2, 14.4	11.9, 14.9	11.8, 15.3	11.4, 15.0	11.4, 15.1	11.0, 15.2
Hematocrit level (%)						
n	10	10	10	10	10	10
Mean	38.85	38.98	40.68	39.04	39.45	38.56
SD	1.927	2.205	2.709	2.804	3.221	2.867
Median	39.60	38.60	41.70	38.90	40.25	39.10
Minimum, Maximum	35.3, 41.4	35.9, 43.9	34.6, 43.7	35.2, 43.5	35.3, 44.1	35.0, 42.6
Neutrophil (/μL)						
n	10	10	10	10	10	10
Mean	3840.6	3896.9	3942.5	4023.7	3842.6	4170.3
SD	1229.97	1055.09	1573.83	1104.14	800.63	1322.88
Median	3648.0	4018.0	3375.5	3619.5	3381.5	4295.0
Minimum, Maximum	1980, 5740	1836, 5390	1820, 6585	2809, 5810	3140, 5047	2014, 5781

Program Name: T080102.sas / Output: t080102_a.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbhm

Table 4.3.4-1 Change in laboratory value: Hematological Tests (In-hospital) (Safety Analysis)
Total cases

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks (or when canceled) N = 10
Lymphocytes (/μL)						
n	10	10	10	10	10	10
Mean	1590.3	1596.8	1720.9	1681.1	1818.2	1561.4
SD	438.00	369.27	544.22	372.48	538.46	493.32
Median	1620.0	1561.0	1729.5	1760.5	1663.0	1388.0
Minimum, Maximum	870, 2186	1130, 2204	1100, 2818	1184, 2192	1219, 2975	1053, 2811

Program Name: T080102.sas / Output: t080102_a.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbhm

Table 4.3.4-1 Change in laboratory value: Hematological Tests (In-hospital) (Safety Analysis)
Cases without co-administration of L-arginine

	0 wks N = 1	4 wks N = 1	12 wks N = 1	24 wks N = 1	36 wks N = 1	52 wks (or when canceled) N = 1
RBC count (10^4/μL)						
n	1	1	1	1	1	1
Mean	469.0	491.0	487.0	499.0	492.0	471.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
WBC count (/μL)						
n	1	1	1	1	1	1
Mean	3220.0	6320.0	5570.0	5240.0	4990.0	4370.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
Blood platelet count (10^4/μL)						
n	1	1	1	1	1	1
Mean	15.70	18.90	16.80	20.50	17.10	18.60
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -

Program Name: T080102.sas / Output: t080102_a.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbhm

Table 4.3.4-1 Change in laboratory value: Hematological Tests (In-hospital) (Safety Analysis)
Cases without co-administration of L-arginine

	0 wks N = 1	4 wks N = 1	12 wks N = 1	24 wks N = 1	36 wks N = 1	52 wks (or when canceled) N = 1
Hemoglobin content (g/dL)						
n	1	1	1	1	1	1
Mean	14.20	14.90	15.30	15.00	15.10	14.10
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
Hematocrit level (%)						
n	1	1	1	1	1	1
Mean	41.40	43.90	43.70	43.50	44.10	41.60
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
Neutrophil (/μL)						
n	1	1	1	1	1	1
Mean	1980.0	4620.0	3890.0	3330.0	3140.0	2660.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -

Program Name: T080102.sas / Output: t080102_a.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbhm

Table 4.3.4-1 Change in laboratory value: Hematological Tests (In-hospital) (Safety Analysis)
Cases without co-administration of L-arginine

	0 wks N = 1	4 wks N = 1	12 wks N = 1	24 wks N = 1	36 wks N = 1	52 wks (or when canceled) N = 1
Lymphocytes (/μL)						
n	1	1	1	1	1	1
Mean	870.0	1130.0	1100.0	1300.0	1290.0	1150.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -

Program Name: T080102.sas / Output: t080102_a.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbhm

Table 4.3.4-1 Change in laboratory value: Hematological Tests (In-hospital) (Safety Analysis)
Cases with co-administration of L-arginine

	0 wks N = 9	4 wks N = 9	12 wks N = 9	24 wks N = 9	36 wks N = 9	52 wks (or when canceled) N = 9
RBC count (10^4/μL)						
n	9	9	9	9	9	9
Mean	439.3	435.4	458.8	450.9	455.0	447.8
SD	24.46	18.45	28.95	32.79	35.17	46.41
Median	441.0	431.0	461.0	451.0	447.0	440.0
Minimum, Maximum	407, 472	407, 465	397, 500	401, 498	412, 514	390, 535
WBC count (/μL)						
n	9	9	9	9	9	9
Mean	6290.0	6082.2	6404.4	6461.1	6548.9	6686.7
SD	1244.15	1409.48	2116.57	1092.59	1212.03	1529.44
Median	6300.0	6600.0	5730.0	6640.0	6100.0	7340.0
Minimum, Maximum	3800, 8250	3400, 7800	3500, 10400	5200, 8300	5300, 8700	3800, 8100
Blood platelet count (10^4/μL)						
n	9	9	9	9	9	9
Mean	26.81	28.57	28.73	28.31	29.07	29.53
SD	7.578	7.790	8.639	8.032	8.215	8.520
Median	22.00	31.20	25.10	29.40	29.10	28.50
Minimum, Maximum	19.6, 38.6	18.5, 38.0	18.1, 43.0	18.6, 39.5	19.1, 41.8	20.6, 43.3

Program Name: T080102.sas / Output: t080102_a.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbhm

Table 4.3.4-1 Change in laboratory value: Hematological Tests (In-hospital) (Safety Analysis)
Cases with co-administration of L-arginine

	0 wks N = 9	4 wks N = 9	12 wks N = 9	24 wks N = 9	36 wks N = 9	52 wks (or when canceled) N = 9
Hemoglobin content (g/dL)						
n	9	9	9	9	9	9
Mean	13.28	13.16	13.67	13.21	13.32	12.93
SD	0.919	0.843	1.084	1.237	1.423	1.568
Median	13.10	13.10	14.10	13.30	13.90	13.20
Minimum, Maximum	12.2, 14.4	11.9, 14.2	11.8, 15.0	11.4, 14.9	11.4, 15.1	11.0, 15.2
Hematocrit level (%)						
n	9	9	9	9	9	9
Mean	38.57	38.43	40.34	38.54	38.93	38.22
SD	1.810	1.453	2.643	2.466	2.944	2.822
Median	39.50	38.40	41.60	38.30	40.00	38.50
Minimum, Maximum	35.3, 40.5	35.9, 41.2	34.6, 42.7	35.2, 42.1	35.3, 42.2	35.0, 42.6
Neutrophil (/μL)						
n	9	9	9	9	9	9
Mean	4047.3	3816.6	3948.3	4100.8	3920.7	4338.1
SD	1105.04	1086.16	1669.18	1142.22	807.82	1285.28
Median	3774.0	3815.0	3365.0	3890.0	3445.0	4366.0
Minimum, Maximum	2356, 5740	1836, 5390	1820, 6585	2809, 5810	3172, 5047	2014, 5781

Program Name: T080102.sas / Output: t080102_a.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbhm

Table 4.3.4-1 Change in laboratory value: Hematological Tests (In-hospital) (Safety Analysis)
Cases with co-administration of L-arginine

	0 wks N = 9	4 wks N = 9	12 wks N = 9	24 wks N = 9	36 wks N = 9	52 wks (or when canceled) N = 9
Lymphocytes (/μL)						
n	9	9	9	9	9	9
Mean	1670.3	1648.7	1789.9	1723.4	1876.9	1607.1
SD	379.16	350.91	528.82	368.67	536.13	500.28
Median	1650.0	1640.0	1785.0	1861.0	1716.0	1408.0
Minimum, Maximum	988, 2186	1190, 2204	1204, 2818	1184, 2192	1219, 2975	1053, 2811

Program Name: T080102.sas / Output: t080102_a.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbhm

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Total cases

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks (or when canceled) N = 10
Total protein (g/dL)						
n	10	10	10	10	10	10
Mean	7.346	7.267	7.327	7.154	7.344	7.157
SD	1.0066	0.7887	0.6049	0.4810	0.6544	0.5089
Median	7.300	7.050	7.150	7.000	7.100	7.100
Minimum, Maximum	6.20, 9.70	6.40, 8.90	6.70, 8.50	6.60, 7.90	6.50, 8.80	6.40, 8.20
Albumin (g/dL)						
n	10	10	10	10	10	10
Mean	4.676	4.553	4.509	4.487	4.601	4.390
SD	0.5253	0.3813	0.3032	0.3024	0.3367	0.1370
Median	4.580	4.565	4.595	4.600	4.600	4.400
Minimum, Maximum	3.90, 5.80	4.00, 5.20	3.90, 4.80	4.00, 4.80	4.20, 5.30	4.20, 4.60
Glucose (mg/dL)						
n	10	10	10	10	10	10
Mean	138.3	116.4	114.7	110.3	113.6	119.0
SD	58.87	34.45	44.48	33.29	37.23	34.10
Median	103.0	103.5	101.5	97.0	100.5	104.5
Minimum, Maximum	88, 252	84, 187	81, 231	85, 195	82, 198	86, 180

Program Name: T080102.sas / Output: t080102_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Total cases

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks (or when canceled) N = 10
HbA1c value (%)						
n	10	10	10	10	10	10
Mean	5.59	5.55	5.71	5.66	5.63	5.67
SD	0.849	0.833	0.975	0.793	0.762	0.906
Median	5.35	5.25	5.35	5.45	5.35	5.40
Minimum, Maximum	4.6, 7.6	4.7, 7.5	4.7, 7.9	4.8, 7.5	4.7, 7.4	4.8, 7.8
AST(GOT) (IU/L)						
n	10	10	10	10	10	10
Mean	21.8	21.3	19.5	25.9	20.3	21.9
SD	11.79	10.18	4.62	19.31	7.44	11.16
Median	20.0	19.5	19.0	21.0	19.0	19.0
Minimum, Maximum	10, 53	12, 48	14, 29	12, 79	13, 39	11, 49
ALT(GPT) (IU/L)						
n	10	10	10	10	10	10
Mean	19.5	17.8	16.5	22.4	18.3	20.8
SD	7.46	7.38	5.48	14.20	7.15	9.93
Median	18.0	17.5	17.5	20.0	19.0	19.0
Minimum, Maximum	10, 34	8, 32	8, 24	7, 54	8, 29	8, 40

Program Name: T080102.sas / Output: t080102_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Total cases

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks (or when canceled) N = 10
ALP (IU/L)						
n	10	10	10	10	10	10
Mean	298.1	299.7	335.7	313.0	303.7	281.2
SD	140.26	134.48	156.30	127.00	91.73	80.42
Median	297.0	293.0	312.0	280.0	303.0	307.5
Minimum, Maximum	138, 601	150, 527	149, 596	162, 556	186, 450	162, 365
LDH (IU/L)						
n	10	10	10	10	10	10
Mean	200.6	203.2	203.6	229.9	190.0	199.9
SD	82.78	57.49	45.47	126.51	47.90	54.73
Median	188.0	193.0	206.0	196.5	188.5	189.0
Minimum, Maximum	120, 420	143, 345	146, 295	142, 583	135, 297	140, 320
γ-GTP (IU/L)						
n	10	10	10	10	10	10
Mean	43.1	48.9	46.1	43.1	55.0	59.0
SD	29.69	37.82	33.82	30.79	43.88	49.05
Median	41.5	43.0	34.5	35.5	40.0	38.5
Minimum, Maximum	12, 96	13, 124	15, 104	15, 102	14, 134	13, 152

Program Name: T080102.sas / Output: t080102_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Total cases

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks (or when canceled) N = 10
CK (U/L)						
n	10	10	10	10	10	10
Mean	176.4	164.6	159.1	447.5	149.8	209.1
SD	178.50	108.51	76.63	992.78	91.14	239.79
Median	128.5	141.0	137.5	110.5	111.5	154.0
Minimum, Maximum	54, 643	72, 391	72, 307	54, 3264	63, 350	86, 883
T-Bil (mg/dL)						
n	10	10	10	10	10	10
Mean	0.453	0.436	0.473	0.533	0.503	0.475
SD	0.3284	0.1876	0.2476	0.3141	0.2884	0.2530
Median	0.350	0.400	0.400	0.450	0.400	0.400
Minimum, Maximum	0.20, 1.30	0.20, 0.80	0.20, 1.10	0.20, 1.30	0.20, 1.10	0.20, 1.00
D-Bil (mg/dL)						
n	10	10	10	10	10	10
Mean	0.100	0.081	0.079	0.111	0.110	0.091
SD	0.0782	0.0582	0.0593	0.0960	0.0699	0.0509
Median	0.100	0.100	0.100	0.100	0.100	0.100
Minimum, Maximum	0.00, 0.30	0.00, 0.20	0.00, 0.20	0.00, 0.30	0.00, 0.20	0.00, 0.20

Program Name: T080102.sas / Output: t080102_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Total cases

	0 wks N = 10	4 wks N = 10	12 wks N = 10	2wks N = 10	36 wks N = 10	52 wks (or when canceled) N = 10
BUN (mg/dL)						
n	10	10	10	10	10	10
Mean	15.82	17.29	16.97	17.13	17.28	17.58
SD	3.609	5.586	6.849	5.963	5.218	4.823
Median	16.00	17.60	17.00	16.85	16.50	17.85
Minimum, Maximum	8.0, 20.8	7.0, 25.2	7.0, 28.7	8.0, 25.7	10.0, 24.8	11.0, 25.3
Cre (mg/dL)						
n	10	10	10	10	10	10
Mean	0.541	0.499	0.511	0.496	0.520	0.542
SD	0.1853	0.1797	0.1896	0.1724	0.2013	0.2446
Median	0.585	0.495	0.530	0.505	0.515	0.530
Minimum, Maximum	0.21, 0.83	0.16, 0.74	0.18, 0.76	0.17, 0.75	0.19, 0.84	0.11, 1.00
eGFR (mL/min/1.73 m^2)						
n	10	10	10	10	10	10
Mean	157.38	177.06	175.49	174.61	171.14	186.44
SD	69.623	86.335	91.962	79.585	83.553	136.868
Median	135.70	152.35	140.05	144.00	145.95	142.65
Minimum, Maximum	88.8, 263.5	77.4, 354.8	82.4, 332.9	92.8, 332.0	74.0, 305.9	54.0, 534.5

Program Name: T080102.sas / Output: t080102_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Total cases

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks (or when canceled) N = 10
uric acid (mg/dL)						
n	10	10	10	10	10	10
Mean	4.490	3.819	3.611	3.575	3.443	3.465
SD	0.8660	0.9153	0.8958	1.1612	0.6238	0.8111
Median	4.450	3.700	3.450	3.550	3.500	3.550
Minimum, Maximum	3.20, 5.90	2.80, 5.59	2.50, 5.31	1.90, 5.70	2.70, 4.43	2.30, 4.85
TG (ng/mL)						
n	10	10	10	10	10	10
Mean	232.7	226.6	248.9	160.1	239.0	138.5
SD	144.73	187.44	274.72	112.08	176.17	71.32
Median	197.5	140.5	157.5	132.0	200.0	126.0
Minimum, Maximum	90, 429	63, 630	56, 969	47, 389	67, 522	46, 320
T-Cho (mg/dL)						
n	10	10	10	10	10	10
Mean	185.0	193.7	185.6	187.5	191.1	178.8
SD	55.82	54.32	50.19	42.58	52.44	55.20
Median	169.5	179.0	180.0	186.0	187.5	162.5
Minimum, Maximum	115, 280	131, 298	114, 276	118, 257	116, 279	120, 304

Program Name: T080102.sas / Output: t080102_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Total cases

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks (or when canceled) N = 10
Na (mEq/L)						
n	10	10	10	10	10	10
Mean	139.0	139.9	138.1	139.5	138.8	139.6
SD	4.11	3.00	4.89	4.81	4.61	3.63
Median	139.0	140.5	139.5	142.0	141.0	140.0
Minimum, Maximum	132, 145	133, 144	126, 142	130, 143	129, 143	132, 143
K (mEq/L)						
n	10	10	10	10	10	10
Mean	4.16	4.28	4.36	4.15	4.11	4.10
SD	0.409	0.388	0.530	0.443	0.338	0.291
Median	4.00	4.20	4.25	4.20	4.10	4.15
Minimum, Maximum	3.9, 5.2	3.8, 5.1	3.9, 5.7	3.3, 4.8	3.7, 4.7	3.6, 4.5
Cl (mEq/L)						
n	10	10	10	10	10	10
Mean	101.4	102.4	101.1	102.2	100.7	101.9
SD	4.22	3.69	4.75	4.76	5.10	4.41
Median	102.5	103.5	102.0	104.0	102.5	102.5
Minimum, Maximum	92, 107	93, 107	90, 106	94, 108	91, 106	94, 108

Program Name: T080102.sas / Output: t080102_b.rtf
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Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases without co-administration of L-arginine

	0 wks N = 1	4 wks N = 1	12 wks N = 1	24 wks N = 1	36 wks N = 1	52 wks (or when canceled) N = 1
Total protein (g/dL)						
n	1	1	1	1	1	1
Mean	7.400	7.400	7.300	7.300	7.400	6.900
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
Albumin (g/dL)						
n	1	1	1	1	1	1
Mean	5.000	4.800	4.600	4.600	4.600	4.400
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
Glucose (mg/dL)						
n	1	1	1	1	1	1
Mean	94.0	94.0	81.0	88.0	82.0	123.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -

Program Name: T080102.sas / Output: t080102_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases without co-administration of L-arginine

	0 wks N = 1	4 wks N = 1	12 wks N = 1	24 wks N = 1	36 wks N = 1	52 wks (or when canceled) N = 1
HbA1cvalue (%)						
n	1	1	1	1	1	1
Mean	5.30	5.20	5.30	5.60	5.30	5.20
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
AST (GOT) (IU/L)						
n	1	1	1	1	1	1
Mean	10.0	14.0	14.0	12.0	13.0	11.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
ALT (GPT) (IU/L)						
n	1	1	1	1	1	1
Mean	12.0	16.0	16.0	14.0	14.0	16.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -

Program Name: T080102.sas / Output: t080102_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases without co-administration of L-arginine

	0 wks N = 1	4 wks N = 1	12 wks N = 1	24 wks N = 1	36 wks N = 1	52 wks (or when canceled) N = 1
ALP (IU/L)						
n	1	1	1	1	1	1
Mean	138.0	150.0	149.0	162.0	186.0	162.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
LDH (IU/L)						
n	1	1	1	1	1	1
Mean	120.0	143.0	146.0	142.0	135.0	140.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
γ-GTP (IU/L)						
n	1	1	1	1	1	1
Mean	12.0	14.0	16.0	16.0	15.0	16.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -

Program Name: T080102.sas / Output: t080102_b.rtf
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Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases without co-administration of L-arginine

	0 wks N = 1	4 wks N = 1	12 wks N = 1	24 wks N = 1	36 wks N = 1	52 wks (or when canceled) N = 1
CK (U/L)						
n	1	1	1	1	1	1
Mean	54.0	74.0	80.0	54.0	74.0	86.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
T-Bil (mg/dL)						
n	1	1	1	1	1	1
Mean	1.300	0.800	1.100	1.300	0.900	0.800
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
D-Bil (mg/dL)						
n	1	1	1	1	1	1
Mean	0.300	0.200	0.200	0.300	0.200	0.200
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -

Program Name: T080102.sas / Output: t080102_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases without co-administration of L-arginine

	0 wks N = 1	4 wks N = 1	12 wks N = 1	24 wks N = 1	36 wks N = 1	52 wks (or when canceled) N = 1
BUN (mg/dL)						
n	1	1	1	1	1	1
Mean	14.00	11.00	8.00	12.00	11.00	11.00
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
Cre (mg/dL)						
n	1	1	1	1	1	1
Mean	0.830	0.740	0.760	0.750	0.840	0.730
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
eGFR (mL/min/1.73 m^2)						
n	1	1	1	1	1	1
Mean	88.80	100.70	97.80	99.20	87.60	102.20
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -

Program Name: T080102.sas / Output: t080102_b.rtf
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Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases without co-administration of L-arginine

	0 wks N = 1	4 wks N = 1	12 wks N = 1	24 wks N = 1	36 wks N = 1	52 wks (or when canceled) N = 1
uric acid (mg/dL)						
n	1	1	1	1	1	1
Mean	5.100	4.100	3.300	3.800	3.800	3.800
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
TG (ng/m)						
n	1	1	1	1	1	1
Mean	97.0	147.0	232.0	150.0	349.0	126.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
T-Cho (mg/dL)						
n	1	1	1	1	1	1
Mean	148.0	153.0	140.0	152.0	149.0	129.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -

Program Name: T080102.sas / Output: t080102_b.rtf
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Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases without co-administration of L-arginine

	0 wks N = 1	4 wks N = 1	12 wks N = 1	24 wks N = 1	36 wks N = 1	52 wks (or when canceled) N = 1
Na (mEq/L)						
n	1	1	1	1	1	1
Mean	145.0	142.0	141.0	141.0	142.0	143.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
K (mEq/L)						
n	1	1	1	1	1	1
Mean	4.00	4.20	3.90	4.20	4.00	3.90
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -
Cl (mEq/L)						
n	1	1	1	1	1	1
Mean	105.0	104.0	103.0	105.0	104.0	106.0
SD	-	-	-	-	-	-
Median	-	-	-	-	-	-
Minimum, Maximum	-, -	-, -	-, -	-, -	-, -	-, -

Program Name: T080102.sas / Output: t080102_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases with co-administration of L-arginine

	0 wks N = 9	4 wks N = 9	12 wks N = 9	24 wks N = 9	36 wks N = 9	52 wks (or when canceled) N = 9
Total protein (g/dL)						
n	9	9	9	9	9	9
Mean	7.340	7.252	7.330	7.138	7.338	7.186
SD	1.0674	0.8350	0.6416	0.5073	0.6938	0.5312
Median	7.200	7.000	7.100	7.000	7.100	7.100
Minimum, Maximum	6.20, 9.70	6.40, 8.90	6.70, 8.50	6.60, 7.90	6.50, 8.80	6.40, 8.20
Albumin (g/dL)						
n	9	9	9	9	9	9
Mean	4.640	4.526	4.499	4.474	4.601	4.389
SD	0.5440	0.3939	0.3198	0.3180	0.3571	0.1453
Median	4.560	4.500	4.590	4.600	4.600	4.400
Minimum, Maximum	3.90, 5.80	4.00, 5.20	3.90, 4.80	4.00, 4.80	4.20, 5.30	4.20, 4.60
Glucose (mg/dL)						
n	9	9	9	9	9	9
Mean	143.2	118.9	118.4	112.8	117.1	118.6
SD	60.22	35.57	45.48	34.32	37.69	36.14
Median	105.0	108.0	102.0	98.0	101.0	99.0
Minimum, Maximum	88, 252	84, 187	81, 231	85, 195	82, 198	86, 180

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Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases with co-administration of L-arginine

	0 wks N = 9	4 wks N = 9	12 wks N = 9	24 wks N = 9	36 wks N = 9	52 wks (or when canceled) N = 9
HbA1cvalue (%)						
n	9	9	9	9	9	9
Mean	5.62	5.59	5.76	5.67	5.67	5.72
SD	0.894	0.874	1.022	0.841	0.798	0.944
Median	5.40	5.30	5.40	5.40	5.40	5.60
Minimum, Maximum	4.6, 7.6	4.7, 7.5	4.7, 7.9	4.8, 7.5	4.7, 7.4	4.8, 7.8
AST (GOT) (IU/L)						
n	9	9	9	9	9	9
Mean	23.1	22.1	20.1	27.4	21.1	23.1
SD	11.71	10.45	4.46	19.82	7.41	11.12
Median	20.0	20.0	19.0	21.0	19.0	19.0
Minimum, Maximum	14, 53	12, 48	14, 29	15, 79	13, 39	12, 49
ALT (GPT) (IU/L)						
n	9	9	9	9	9	9
Mean	20.3	18.0	16.6	23.3	18.8	21.3
SD	7.40	7.79	5.81	14.73	7.41	10.38
Median	19.0	18.0	18.0	20.0	19.0	20.0
Minimum, Maximum	10, 34	8, 32	8, 24	7, 54	8, 29	8, 40

Program Name: T080102.sas / Output: t080102_b.rtf
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Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases with co-administration of L-arginine

	0 wks N = 9	4 wks N = 9	12 wks N = 9	24 wks N = 9	36 wks N = 9	52 wks (or when canceled) N = 9
ALP (IU/L)						
n	9	9	9	9	9	9
Mean	315.9	316.3	356.4	329.8	316.8	294.4
SD	136.28	131.28	150.48	122.39	86.85	72.82
Median	303.0	294.0	337.0	284.0	344.0	336.0
Minimum, Maximum	166, 601	167, 527	197, 596	208, 556	190, 450	183, 365
LDH (IU/L)						
n	9	9	9	9	9	9
Mean	209.6	209.9	210.0	239.7	196.1	206.6
SD	82.50	56.70	43.19	130.12	46.49	53.58
Median	196.0	203.0	211.0	201.0	200.0	192.0
Minimum, Maximum	133, 420	154, 345	149, 295	166, 583	140, 297	144, 320
γ-GTP (IU/L)						
n	9	9	9	9	9	9
Mean	46.6	52.8	49.4	46.1	59.4	63.8
SD	29.28	37.94	34.07	31.06	44.09	49.49
Median	56.0	60.0	49.0	51.0	58.0	54.0
Minimum, Maximum	13, 96	13, 124	15, 104	15, 102	14, 134	13, 152

Program Name: T080102.sas / Output: t080102_b.rtf
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Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases with co-administration of L-arginine

	0 wks N = 9	4 wks N = 9	12 wks N = 9	24 wks N = 9	36 wks N = 9	52 wks (or when canceled) N = 9
CK (U/L)						
n	9	9	9	9	9	9
Mean	190.0	174.7	167.9	491.2	158.2	222.8
SD	183.75	110.02	75.74	1042.75	92.45	250.16
Median	139.0	160.0	138.0	127.0	115.0	162.0
Minimum, Maximum	63, 643	72, 391	72, 307	73, 3264	63, 350	88, 883
T-Bil (mg/dL)						
n	9	9	9	9	9	9
Mean	0.359	0.396	0.403	0.448	0.459	0.439
SD	0.1473	0.1455	0.1198	0.1712	0.2678	0.2395
Median	0.300	0.400	0.400	0.400	0.400	0.400
Minimum, Maximum	0.20, 0.60	0.20, 0.70	0.20, 0.60	0.20, 0.70	0.20, 1.10	0.20, 1.00
D-Bil (mg/dL)						
n	9	9	9	9	9	9
Mean	0.078	0.068	0.066	0.090	0.100	0.079
SD	0.0363	0.0429	0.0439	0.0735	0.0661	0.0355
Median	0.100	0.100	0.100	0.100	0.100	0.100
Minimum, Maximum	0.00, 0.10	0.00, 0.10	0.00, 0.10	0.00, 0.20	0.00, 0.20	0.00, 0.10

Program Name: T080102.sas / Output: t080102_b.rtf
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Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases with co-administration of L-arginine

	0 wks N = 9	4 wks N = 9	12 wks N = 9	24 wks N = 9	36 wks N = 9	52 wks (or when canceled) N = 9
BUN (mg/dL)						
n	9	9	9	9	9	9
Mean	16.02	17.99	17.97	17.70	17.98	18.31
SD	3.768	5.441	6.449	6.029	5.016	4.490
Median	17.00	18.20	18.00	17.50	18.00	20.00
Minimum, Maximum	8.0, 20.8	7.0, 25.2	7.0, 28.7	8.0, 25.7	10.0, 24.8	13.0, 25.3
Cre (mg/dL)						
n	9	9	9	9	9	9
Mean	0.509	0.472	0.483	0.468	0.484	0.521
SD	0.1644	0.1681	0.1784	0.1565	0.1771	0.2498
Median	0.570	0.490	0.530	0.470	0.460	0.520
Minimum, Maximum	0.21, 0.72	0.16, 0.72	0.18, 0.68	0.17, 0.68	0.19, 0.75	0.11, 1.00
eGFR (mL/min/1.73 m^2)						
n	9	9	9	9	9	9
Mean	165.00	185.54	184.12	182.99	180.42	195.80
SD	69.283	87.038	93.145	79.597	82.973	141.735
Median	137.90	155.70	143.30	160.30	151.30	151.30
Minimum, Maximum	89.5, 263.5	77.4, 354.8	82.4, 332.9	92.8, 332.0	74.0, 305.9	54.0, 534.5

Program Name: T080102.sas / Output: t080102_b.rtf
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Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases with co-administration of L-arginine

	0 wks N = 9	4 wks N = 9	12 wks N = 9	24 wks N = 9	36 wks N = 9	52 wks (or when canceled) N = 9
uric acid (mg/dL)						
n	9	9	9	9	9	9
Mean	4.422	3.788	3.646	3.550	3.403	3.428
SD	0.8899	0.9652	0.9431	1.2288	0.6482	0.8511
Median	4.300	3.600	3.600	3.400	3.400	3.500
Minimum, Maximum	3.20, 5.90	2.80, 5.59	2.50, 5.31	1.90, 5.70	2.70, 4.43	2.30, 4.85
TG (ng/mL)						
n	9	9	9	9	9	9
Mean	247.8	235.4	250.8	161.2	226.8	139.9
SD	144.94	196.59	291.32	118.82	182.30	75.50
Median	270.0	134.0	104.0	114.0	125.0	126.0
Minimum, Maximum	90, 429	63, 630	56, 969	47, 389	67, 522	46, 320
T-Cho (mg/dL)						
n	9	9	9	9	9	9
Mean	189.1	198.2	190.7	191.4	195.8	184.3
SD	57.57	55.58	50.45	43.18	53.37	55.53
Median	188.0	188.0	183.0	194.0	194.0	172.0
Minimum, Maximum	115, 280	131, 298	114, 276	118, 257	116, 279	120, 304

Program Name: T080102.sas / Output: t080102_b.rtf
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Data Source: adlbbe

Table 4.3.4-2 Change in laboratory value: Biochemical Test (In-hospital) (Safety Analysis)
Cases with co-administration of L-arginine

	0 wks N = 9	4 wks N = 9	12 wks N = 9	24 wks N = 9	36 wks N = 9	52 wks (or when canceled) N = 9
Na (mEq/L)						
n	9	9	9	9	9	9
Mean	138.3	139.7	137.8	139.3	138.4	139.2
SD	3.74	3.08	5.07	5.07	4.75	3.63
Median	138.0	140.0	139.0	142.0	141.0	140.0
Minimum, Maximum	132, 144	133, 144	126, 142	130, 143	129, 143	132, 143
K (mEq/L)						
n	9	9	9	9	9	9
Mean	4.18	4.29	4.41	4.14	4.12	4.12
SD	0.429	0.411	0.535	0.469	0.356	0.299
Median	4.00	4.20	4.30	4.20	4.20	4.20
Minimum, Maximum	3.9, 5.2	3.8, 5.1	3.9, 5.7	3.3, 4.8	3.7, 4.7	3.6, 4.5
Cl (mEq/L)						
n	9	9	9	9	9	9
Mean	101.0	102.2	100.9	101.9	100.3	101.4
SD	4.27	3.87	4.99	4.94	5.27	4.42
Median	102.0	103.0	102.0	104.0	102.0	102.0
Minimum, Maximum	92, 107	93, 107	90, 106	94, 108	91, 106	94, 108

Program Name: T080102.sas / Output: t080102_b.rtf
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Data Source: adlbbe

Table 4.3.4-3 List of hematological examinations (Safety Analysis) No. 1

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	RBC count (10^4/μL) measure-ment	RBC count (10^4/μL) Abnormal / Abnormal change	WBC count (/μL) measure-ment	WBC count (/μL) Abnormal / Abnormal change	Blood platelet count (10^4/μL) measure-ment	Blood platelet count (10^4/μL) Abnormal / Abnormal change	Hemoglobin content (g/dL) measure-ment	Hemoglobin content (g/dL) Abnormal / Abnormal change
KN-01-01, with co-administration of L-arginine											
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	465		8250		38.6	yes	12.2	
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	460		7380		37.4	yes	11.9	
12 wks	2013/12/26 08:30	2013/12/26 07:15	2013/12/26 09:30	484	yes	5730		43	yes	11.8	
24 wks	2014/03/20 06:50	2014/03/20 07:10	2014/03/20 09:10	498	yes	6640		38.8	yes	11.4	yes
36 wks	2014/06/12 06:45	2014/06/12 07:05	2014/06/12 08:40	514	yes	7900		41.8	yes	11.4	yes
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	535	yes	7340		43.3	yes	11	yes
KN-03-01, with co-administration of L-arginine											
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	455		6000		38.4		14.1	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	443		5500		34		13.9	
12 wks	2014/03/31 08:00	2014/03/31 08:40	2014/03/31 09:51	468		5800		37		14.4	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	439		5900		34.1		13.6	
24 wks	2014/06/09 08:00	2014/06/09 08:15	2014/06/09 09:30	464		5400		39.5		14.3	
36 wks	2014/09/01 07:50	2014/09/01 08:10	2014/09/01 10:00	445		5300		33.9		14.3	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	455		6100		37.1		14.4	

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Data Source: adlbhm

Table 4.3.4-3 List of hematological examinations (Safety Analysis) No. 1

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	RBC count (10^4/μL) measure-ment	RBC count (10^4/μL) Abnormal / Abnormal change	WBC count (/μL) measure-ment	WBC count (/μL) Abnormal / Abnormal change	Blood platelet count (10^4/μL) measure-ment	Blood platelet count (10^4/μL) Abnormal / Abnormal change	Hemoglobin content (g/dL) measure-ment	Hemoglobin content (g/dL) Abnormal / Abnormal change
KN-04-01, without co-administration of L-arginine											
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	469		3220		15.7		14.2	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	491		6320		18.9		14.9	
12 wks	2014/02/06 12:30	2014/02/06 12:30	2014/02/06 13:40	487		5570		16.8		15.3	
24 wks	2014/05/09 11:30	2014/05/09 11:45	2014/05/09 14:58	499		5240		20.5		15	
36 wks	2014/07/18 12:30	2014/07/18 12:40	2014/07/18 14:15	492		4990		17.1		15.1	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	471		4370		18.6		14.1	
KN-05-01, with co-administration of L-arginine											
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	425		5600		20.6		14.2	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	431		5300		20.9		14.2	
12 wks	2014/01/24 08:20	2014/01/24 08:30	2014/01/24 10:49	438		5100		20.9		14.3	
24 wks	2014/04/18 07:30	2014/04/18 07:50	2014/04/18 10:14	451		5300		20.4		14.6	
36 wks	2014/07/04 08:20	2014/07/04 08:29	2014/07/04 11:15	447		6100		19.7		14.6	
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	423		6400		23.4		14.2	

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Data Source: adlbhm

Table 4.3.4-3 List of hematological examinations (Safety Analysis) No. 1

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	RBC count (10^4/μL) measure-ment	RBC count (10^4/μL) Abnormal / Abnormal change	WBC count (/μL) measure-ment	WBC count (/μL) Abnormal / Abnormal change	Blood platelet count (10^4/μL) measure-ment	Blood platelet count (10^4/μL) Abnormal / Abnormal change	Hemoglobin content (g/dL) measure-ment	Hemoglobin content (g/dL) Abnormal / Abnormal change
KN-07-01, with co-administration of L-arginine											
0 wks	2013/10/31 11:55	-	2013/10/31 13:35	407		7000		30.6		12.2	
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	428		7800		38	yes	12.7	
12 wks	2014/01/24 07:00	2014/01/24 07:00	2014/01/24 11:47	461		8000		38.4	yes	13.2	
24 wks	2014/04/18 09:00	2014/04/17 20:00	2014/04/18 14:10	452		6900		32.4		12.7	
36 wks	2014/07/18 07:00	2014/07/18 07:00	2014/07/18 11:02	418		6000		38	yes	11.7	
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	409		8100		39.3	yes	11.1	yes
KN-08-01, with co-administration of L-arginine											
0 wks	2013/10/28 12:10	-	2013/10/28 13:40	441		6600		21.3		13.1	
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	421		4900		20.4		12.6	yes
12 wks	2014/01/22 07:40	2014/01/22 08:15	2014/01/22 10:30	464		5100		24.6		13.9	
unscheduled test	2014/03/18 18:00	2014/03/18 18:20	2014/03/19 06:00	454		18000	yes yes	23.7		13.6	
unscheduled test	2014/03/23 18:00	2014/03/23 18:15	2014/03/24 06:00	435		5700		23.6		13	
24 wks	2014/04/16 07:40	2014/04/16 08:15	2014/04/16 10:50	449		5200		18.6		13.5	
36 wks	2014/07/09 07:40	2014/07/09 08:25	2014/07/09 10:40	459		7200		23.6		13.9	
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	442		7400		20.6		13.8	

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Table 4.3.4-3 List of hematological examinations (Safety Analysis) No. 1

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	RBC count (10^4/μL) measure-ment	RBC count (10^4/μL) Abnormal / Abnormal change	WBC count (/μL) measure-ment	WBC count (/μL) Abnormal / Abnormal change	Blood platelet count (10^4/μL) measure-ment	Blood platelet count (10^4/μL) Abnormal / Abnormal change	Hemoglobin content (g/dL) measure-ment	Hemoglobin content (g/dL) Abnormal / Abnormal change
KN-10-01, with co-administration of L-arginine											
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	457		6300		22		14.1	
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	426		6600		33.6		13.1	yes
12 wks	2014/01/29 13:10	2014/01/29 13:30	2014/01/29 14:45	460		10400	yes yes	27.9		14.1	
24 wks	2014/04/23 12:15	2014/04/23 12:45	2014/04/23 14:35	414	yes	8300		31.8		12.4	yes
36 wks	2014/07/23 12:00	2014/07/23 12:50	2014/07/23 14:20	459		8700		33.5		14	
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	390	yes	8100		30		11.9	yes
KN-11-01, with co-administration of L-arginine											
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	407	yes	5800		28.4		12.5	yes
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	438		7000		31.2		13.5	yes
12 wks	2014/02/25 08:00	2014/02/25 08:30	2014/02/25 10:30	457		5600		25.1		14.2	
24 wks	2014/05/26 07:30	2014/05/26 07:45	2014/05/26 10:46	433		5800		29.4		13.3	yes
36 wks	2014/08/18 07:10	2014/08/18 07:22	2014/08/18 10:50	435		5500		29.1		13.4	yes
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	428	yes	4900		28.5		13.2	yes

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Table 4.3.4-3 List of hematological examinations (Safety Analysis) No. 1

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	RBC count (10^4/μL) measure-ment	RBC count (10^4/μL) Abnormal / Abnormal change	WBC count (/μL) measure-ment	WBC count (/μL) Abnormal / Abnormal change	Blood platelet count (10^4/μL) measure-ment	Blood platelet count (10^4/μL) Abnormal / Abnormal change	Hemoglobin content (g/dL) measure-ment	Hemoglobin content (g/dL) Abnormal / Abnormal change
KN-12-01, with co-administration of L-arginine											
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	425		3800		21.8		12.7	
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	407		3400	yes	23.1		12.3	
12 wks	2014/02/10 07:00	2014/02/10 08:00	2014/02/10 11:50	397		3500		23.6		12.1	
24 wks	2014/04/27 18:30	2014/04/28 10:00	2014/04/28 12:00	401		7400		24.5		11.8	
36 wks	2014/07/27 18:30	2014/07/28 08:30	2014/07/28 11:50	412		5300		22.9		11.5	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	440		3800		22.1		11.6	
KN-13-01, with co-administration of L-arginine											
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	472		7260		19.6		14.4	
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	465		6860		18.5		14.2	
unscheduled test	2014/02/10 12:30	2014/02/10 13:00	2014/02/10 14:22	494		11400	yes yes	19.8		15.2	
12 wks	2014/03/14 12:30	2014/03/14 13:30	2014/03/14 13:53	500		8410		18.1		15	
24 wks	2014/05/30 11:30	2014/05/30 12:00	2014/05/30 13:48	496		7210		19.4		14.9	
36 wks	2014/08/22 12:00	2014/08/22 12:00	2014/08/22 12:38	506		6940		19.1		15.1	
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:05	508		8040		21.5		15.2	

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Table 4.3.4-3 List of hematological examinations (Safety Analysis) No. 2

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Hematocrit level (%) measure-ment	Hematocrit level (%) Abnormal / Abnormal change	Neutrophil (/μL) measure-ment	Neutrophil (/μL) Abnormal / Abnormal change	Lymphocytes (/μL) measure-ment	Lymphocytes (/μL) Abnormal / Abnormal change
KN-01-01, with co-administration of L-arginine									
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	38		5740		1650	
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	37.3		4890		1640	
12 wks	2013/12/26 08:30	2013/12/26 07:15	2013/12/26 09:30	37.4		3170		1860	
24 wks	2014/03/20 06:50	2014/03/20 07:10	2014/03/20 09:10	36.5		3890		1920	
36 wks	2014/06/12 06:45	2014/06/12 07:05	2014/06/12 08:40	36.2		4800		1610	
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	36.2		4800		1660	
KN-03-01, with co-administration of L-arginine									
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	40.1		3522		1806	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	38.3	yes	3718		1221	
12 wks	2014/03/31 08:00	2014/03/31 08:40	2014/03/31 09:51	42		3062		2169	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	38.5	yes	3735		1457	
24 wks	2014/06/09 08:00	2014/06/09 08:15	2014/06/09 09:30	39.5	yes	2830		1922	
36 wks	2014/09/01 07:50	2014/09/01 08:10	2014/09/01 10:00	40		3228		1548	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	40.1		3593		1763	

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Table 4.3.4-3 List of hematological examinations (Safety Analysis) No. 2

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Hematocrit level (%) measure-ment	Hematocrit level (%) Abnormal / Abnormal change	Neutrophil (/μL) measure-ment	Neutrophil (/μL) Abnormal / Abnormal change	Lymphocytes (/μL) measure-ment	Lymphocytes (/μL) Abnormal / Abnormal change
KN-04-01, without co-administration of L-arginine									
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	41.4		1980		870	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	43.9		4620		1130	yes
12 wks	2014/02/06 12:30	2014/02/06 12:30	2014/02/06 13:40	43.7		3890		1100	yes
24 wks	2014/05/09 11:30	2014/05/09 11:45	2014/05/09 14:58	43.5		3330		1300	
36 wks	2014/07/18 12:30	2014/07/18 12:40	2014/07/18 14:15	44.1		3140		1290	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	41.6		2660		1150	
KN-05-01, with co-administration of L-arginine									
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	39.5		3416	yes	1848	yes
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	41.2		3021		1855	yes
12 wks	2014/01/24 08:20	2014/01/24 08:30	2014/01/24 10:49	41.6		2805		1785	yes
24 wks	2014/04/18 07:30	2014/04/18 07:50	2014/04/18 10:14	42.1		2809		2120	
36 wks	2014/07/04 08:20	2014/07/04 08:29	2014/07/04 11:15	41.7		3172		2379	
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	39.7	yes	4224		1408	

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Table 4.3.4-3 List of hematological examinations (Safety Analysis) No. 2

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Hematocrit level (%) measure-ment	Hematocrit level (%) Abnormal / Abnormal change	Neutrophil (/μL) measure-ment	Neutrophil (/μL) Abnormal / Abnormal change	Lymphocytes (/μL) measure-ment	Lymphocytes (/μL) Abnormal / Abnormal change
KN-07-01, with co-administration of L-arginine									
0 wks	2013/10/31 11:55	-	2013/10/31 13:35	37		4585		1463	
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	38.4		5390		1482	yes
12 wks	2014/01/24 07:00	2014/01/24 07:00	2014/01/24 11:47	40.6		4800		2096	
24 wks	2014/04/18 09:00	2014/04/17 20:00	2014/04/18 14:10	38.3		5051	yes	1290	yes
36 wks	2014/07/18 07:00	2014/07/18 07:00	2014/07/18 11:02	35.6		3318		1830	
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	35		4366		2811	
KN-08-01, with co-administration of L-arginine									
0 wks	2013/10/28 12:10	-	2013/10/28 13:40	40		4825	yes	1360	yes
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	38.8	yes	2999		1446	
12 wks	2014/01/22 07:40	2014/01/22 08:15	2014/01/22 10:30	42.7		3386	yes	1204	yes
unscheduled test	2014/03/18 18:00	2014/03/18 18:20	2014/03/19 06:00	41.6		16092	yes yes	1098	yes
unscheduled test	2014/03/23 18:00	2014/03/23 18:15	2014/03/24 06:00	39.5		3659		1454	
24 wks	2014/04/16 07:40	2014/04/16 08:15	2014/04/16 10:50	40.1		3349		1362	
36 wks	2014/07/09 07:40	2014/07/09 08:25	2014/07/09 10:40	42.2		5047	yes	1498	yes
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	41.1		5557	yes	1362	yes

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Data Source: adlbhm

Table 4.3.4-3 List of hematological examinations (Safety Analysis) No. 2

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Hematocrit level (%) measure-ment	Hematocrit level (%) Abnormal / Abnormal change	Neutrophil (/μL) measure-ment	Neutrophil (/μL) Abnormal / Abnormal change		Lymphocytes (/μL) measure-ment	Lymphocytes (/μL) Abnormal / Abnormal change	
KN-10-01, with co-administration of L-arginine											
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	40.5		3774	yes		2142		
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	37.8	yes	3815	yes		2204		
12 wks	2014/01/29 13:10	2014/01/29 13:30	2014/01/29 14:45	41.8		6542	yes		2818	yes	
24 wks	2014/04/23 12:15	2014/04/23 12:45	2014/04/23 14:35	36.1	yes	5810	yes	yes	1660	yes	yes
36 wks	2014/07/23 12:00	2014/07/23 12:50	2014/07/23 14:20	40.5		4863	yes		2975		
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	35.2	yes	5670	yes	yes	1053	yes	yes
KN-11-01, with co-administration of L-arginine											
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	35.3	yes	3010			2186		
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	38.9	yes	4221			2051	yes	
12 wks	2014/02/25 08:00	2014/02/25 08:30	2014/02/25 10:30	40.6		3365			1674	yes	
24 wks	2014/05/26 07:30	2014/05/26 07:45	2014/05/26 10:46	37.4	yes	3335			1861		
36 wks	2014/08/18 07:10	2014/08/18 07:22	2014/08/18 10:50	36.7	yes	3173			1716		
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	38.5	yes	3038			1367	yes	

Program Name: L080102_01.sas / Output: l080102_01_a.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbhm

Table 4.3.4-3 List of hematological examinations (Safety Analysis) No. 2

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Hematocrit level (%) measure-ment	Hematocrit level (%) Abnormal / Abnormal change	Neutrophil (/μL) measure-ment	Neutrophil (/μL) Abnormal / Abnormal change	Lymphocytes (/μL) measure-ment	Lymphocytes (/μL) Abnormal / Abnormal change
KN-12-01, with co-administration of L-arginine									
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	37		2356		988	
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	35.9		1836		1190	
12 wks	2014/02/10 07:00	2014/02/10 08:00	2014/02/10 11:50	34.6		1820		1225	
24 wks	2014/04/27 18:30	2014/04/28 10:00	2014/04/28 12:00	35.2		5550	yes	1184	yes
36 wks	2014/07/27 18:30	2014/07/28 08:30	2014/07/28 11:50	35.3		3445		1219	yes
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	35.6		2014		1368	
KN-13-01, with co-administration of L-arginine									
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	39.7	yes	5198	yes	1590	yes
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	39.3	yes	4459	yes	1749	yes
unscheduled test	2014/02/10 12:30	2014/02/10 13:00	2014/02/10 14:22	41.7		9553	yes	1140	yes
12 wks	2014/03/14 12:30	2014/03/14 13:30	2014/03/14 13:53	41.8		6585	yes	1278	yes
24 wks	2014/05/30 11:30	2014/05/30 12:00	2014/05/30 13:48	41.7		4283		2192	
36 wks	2014/08/22 12:00	2014/08/22 12:00	2014/08/22 12:38	42.2		4240		2117	
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:05	42.6		5781		1672	yes

Program Name: L080102_01.sas / Output: l080102_01_a.rtf
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Data Source: adlbhm

Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.1

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Total protein (g/dL) mesure-ment	Total protein (g/dL) Abnormal / Abnormal change	Albumin (g/dL) mesure-ment	Albumin (g/dL) Abnormal / Abnormal change	Glucose (mg/dL) mesure-ment	Glucose (mg/dL) Abnormal / Abnormal change	HbA1c value (%) mesure-ment	HbA1c value (%) Abnormal / Abnormal change
KN-01-01, with co-administration of L-arginine											
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	6.9		4.3		91		5.4	
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	6.6		4		99		5.3	
12 wks	2013/12/26 08:30	2013/12/26 07:15	2013/12/26 09:30	6.8		3.9		102		5.7	
24 wks	2014/03/20 06:50	2014/03/20 07:10	2014/03/20 09:10	6.8		4.1		132	yes	5.5	
36 wks	2014/06/12 06:45	2014/06/12 07:05	2014/06/12 08:40	7.1		4.2		134	yes	5.7	
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	7.1		4.3		110		5.7	
KN-03-01, with co-administration of L-arginine											
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	6.7		4.6		98		4.9	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	6.5		4.3		99		4.9	
12 wks	2014/03/31 08:00	2014/03/31 08:40	2014/03/31 09:51	6.7		4.5		110		4.9	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	6.1	yes	4.2		107		4.9	
24 wks	2014/06/09 08:00	2014/06/09 08:15	2014/06/09 09:30	6.9		4.7		98		4.9	
36 wks	2014/09/01 07:50	2014/09/01 08:10	2014/09/01 10:00	6.5		4.4		107		4.7	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	6.8		4.6		93		4.8	

Program Name: L080102_01.sas / Output: l080102_01_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.1

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Total protein (g/dL) mesure-ment	Total protein (g/dL) Abnormal / Abnormal change	Albumin (g/dL) mesure-ment	Albumin (g/dL) Abnormal / Abnormal change	Glucose (mg/dL) mesure-ment	Glucose (mg/dL) Abnormal / Abnormal change	HbA1c value (%) mesure-ment	HbA1c value (%) Abnormal / Abnormal change
KN-04-01, without co-administration of L-arginine											
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	7.4		5	yes	94		5.3	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	7.4		4.8		94		5.2	
12 wks	2014/02/06 12:30	2014/02/06 12:30	2014/02/06 13:40	7.3		4.6		81		5.3	
24 wks	2014/05/09 11:30	2014/05/09 11:45	2014/05/09 14:58	7.3		4.6		88		5.6	
36 wks	2014/07/18 12:30	2014/07/18 12:40	2014/07/18 14:15	7.4		4.6		82		5.3	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	6.9		4.4		123	yes	5.2	
KN-05-01, with co-administration of L-arginine											
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	7.2		5.1	yes	210	yes	5.1	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	7.1		4.9		87		5.1	
12 wks	2014/01/24 08:20	2014/01/24 08:30	2014/01/24 10:49	7.1		4.8		91		5.3	
24 wks	2014/04/18 07:30	2014/04/18 07:50	2014/04/18 10:14	7		4.8		87		5.3	
36 wks	2014/07/04 08:20	2014/07/04 08:29	2014/07/04 11:15	7.1		5		84		5.3	
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	6.8		4.5		86		5.2	

Program Name: L080102_01.sas / Output: l080102_01_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.1

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Total protein (g/dL) mesure-ment	Total protein (g/dL) Abnormal / Abnormal change	Albumin (g/dL) mesure-ment	Albumin (g/dL) Abnormal / Abnormal change	Glucose (mg/dL) mesure-ment	Glucose (mg/dL) Abnormal / Abnormal change	HbA1c value (%) mesure-ment	HbA1c value (%) Abnormal / Abnormal change
KN-07-01, with co-administration of L-arginine											
0 wks	2013/10/31 11:55	-	2013/10/31 13:35	6.3		4.3		173	yes	6.2	
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	6.9		4.7		123	yes	6.1	
12 wks	2014/01/24 07:00	2014/01/24 07:00	2014/01/24 11:47	7.2		4.8		95		6.8	yes
24 wks	2014/04/18 09:00	2014/04/17 20:00	2014/04/18 14:10	7		4.6		114	yes	6.4	yes
36 wks	2014/07/18 07:00	2014/07/18 07:00	2014/07/18 11:02	6.9		4.6		97		6.1	
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	6.4		4.2		177	yes	6.5	yes
KN-08-01, with co-administration of L-arginine											
0 wks	-	-	2013/10/28 11:50					88		5.3	
0 wks	2013/10/28 12:10	-	2013/10/28 13:40	6.2	yes	3.9					
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	6.4	yes	4		84		5.2	
12 wks	2014/01/22 07:40	2014/01/22 08:15	2014/01/22 10:30	6.8		4.1		81		5.1	
unscheduled test	2014/03/18 18:00	2014/03/18 18:20	2014/03/19 06:00	7		4					
24 wks	2014/04/16 07:40	2014/04/16 08:15	2014/04/16 10:50	6.6	yes	4		85		5.3	
36 wks	2014/07/09 07:40	2014/07/09 08:25	2014/07/09 10:40	7		4.2		82		5.4	
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	7.2		4.3		95		5.6	

Program Name: L080102_01.sas / Output: l080102_01_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.1

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Total protein (g/dL) mesure-ment	Total protein (g/dL) Abnormal / Abnormal change	Albumin (g/dL) mesure-ment	Albumin (g/dL) Abnormal / Abnormal change	Glucose (mg/dL) mesure-ment	Glucose (mg/dL) Abnormal / Abnormal change	HbA1c value (%) mesure-ment	HbA1c value (%) Abnormal / Abnormal change
KN-10-01, with co-administration of L-arginine											
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	9.7	yes	5.8	yes	101		5.5	
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	8.9	yes	5.2	yes	116	yes	5.3	
12 wks	2014/01/29 13:10	2014/01/29 13:30	2014/01/29 14:45	8.5	yes	4.8		114	yes	5.4	
24 wks	2014/04/23 12:15	2014/04/23 12:45	2014/04/23 14:35	7.9		4.8		114	yes	5.4	
36 wks	2014/07/23 12:00	2014/07/23 12:50	2014/07/23 14:20	8.8	yes	5.3	yes	100		5.3	
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	8.2		4.5		99		5	
KN-11-01, with co-administration of L-arginine											
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	7.66		4.56		105		4.6	
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	7.97		4.63		108		4.7	
12 wks	2014/02/25 08:00	2014/02/25 08:30	2014/02/25 10:30	7.77		4.59		101		4.7	
24 wks	2014/05/26 07:30	2014/05/26 07:45	2014/05/26 10:40	7.64		4.57		94		4.8	
36 wks	2014/08/18 07:10	2014/08/18 07:22	2014/08/18 10:50	7.74		4.61		101		5	
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	7.37		4.2		98		5	

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Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.1

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Total protein (g/dL) mesure-ment	Total protein (g/dL) Abnormal / Abnormal change	Albumin (g/dL) mesure-ment	Albumin (g/dL) Abnormal / Abnormal change	Glucose (mg/dL) mesure-ment	Glucose (mg/dL) Abnormal / Abnormal change	HbA1c value (%) mesure-ment	HbA1c value (%) Abnormal / Abnormal change
KN-12-01, with co-administration of L-arginine											
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	7.4		4.7		171	yes	6	
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	7		4.5		167	yes	6.2	
12 wks	2014/02/10 07:00	2014/02/10 08:00	2014/02/10 11:50	7		4.4		141	yes	6	
24 wks	2014/04/27 18:30	2014/04/28 10:00	2014/04/28 12:00	6.6	yes	4.1		96		5.9	
36 wks	2014/07/27 18:30	2014/07/28 08:30	2014/07/28 11:50	7		4.5		151	yes	6.1	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	7.1		4.4		129	yes	5.9	
KN-13-01, with co-administration of L-arginine											
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	8		4.5		252	yes	7.6	yes
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	7.9		4.5		187	yes	7.5	yes
unscheduled test	2014/02/10 12:30	2014/02/10 13:00	2014/02/10 14:22	8.4	yes	4.9		211	yes		
12 wks	2014/03/14 12:30	2014/03/14 13:30	2014/03/14 13:53	8.1		4.6		231	yes	7.9	yes
24 wks	2014/05/30 11:30	2014/05/30 12:00	2014/05/30 13:48	7.8		4.6		195	yes	7.5	yes
36 wks	2014/08/22 12:00	2014/08/22 12:00	2014/08/22 12:38	7.9		4.6		198	yes	7.4	yes
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:11	7.7		4.5		180	yes	7.8	yes

Program Name: L080102_01.sas / Output: l080102_01_b.rtf
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Data Source: adlbbe

Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.2

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	AST(GOT) (IU/L) mesure-ment	AST(GOT) (IU/L) Abnormal / Abnormal change	ALT(GPT) (IU/L) mesure-ment	ALT(GPT) (IU/L) Abnormal / Abnormal change	ALP (IU/L) mesure-ment	ALP (IU/L) Abnormal / Abnormal change	LDH (IU/L) mesure-ment	LDH (IU/L) Abnormal / Abnormal change
KN-01-01, with co-administration of L-arginine											
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	20		20		212		196	
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	21		17		193		211	
12 wks	2013/12/26 08:30	2013/12/26 07:15	2013/12/26 09:30	22		21		227		231	
24 wks	2014/03/20 06:50	2014/03/20 07:10	2014/03/20 09:10	24		31		220		201	
36 wks	2014/06/12 06:45	2014/06/12 07:05	2014/06/12 08:40	19		23		234		200	
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	25		40		242		237	
KN-03-01, with co-administration of L-arginine											
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	25		30		340		204	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	19		18		320		183	
12 wks	2014/03/31 08:00	2014/03/31 08:40	2014/03/31 09:51	19		17		337		213	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	33	yes	18		279		244	yes
24 wks	2014/06/09 08:00	2014/06/09 08:15	2014/06/09 09:30	29		35		320		227	yes
36 wks	2014/09/01 07:50	2014/09/01 08:10	2014/09/01 10:00	19		19		346	yes	177	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	19		26		356	yes	203	

Program Name: L080102_01.sas / Output: l080102_01_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.2

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	AST(GOT) (IU/L) mesure-ment	AST(GOT) (IU/L) Abnormal / Abnormal change	ALT(GPT) (IU/L) mesure-ment	ALT(GPT) (IU/L) Abnormal / Abnormal change	ALP (IU/L) mesure-ment	ALP (IU/L) Abnormal / Abnormal change	LDH (IU/L) mesure-ment	LDH (IU/L) Abnormal / Abnormal change
KN-04-01, without co-administration of L-arginine											
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	10	yes	12		138		120	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	14		16		150		143	
12 wks	2014/02/06 12:30	2014/02/06 12:30	2014/02/06 13:40	14		16		149		146	
24 wks	2014/05/09 11:30	2014/05/09 11:45	2014/05/09 14:58	12	yes	14		162		142	
36 wks	2014/07/18 12:30	2014/07/18 12:40	2014/07/18 14:15	13		14		186		135	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	11	yes	16		162		140	
KN-05-01, with co-administration of L-arginine											
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	22		17		315		206	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	25		18		292		239	yes
12 wks	2014/01/24 08:20	2014/01/24 08:30	2014/01/24 10:49	24		18		287		239	yes
24 wks	2014/04/18 07:30	2014/04/18 07:50	2014/04/18 10:14	24		20		276		208	
36 wks	2014/07/04 08:20	2014/07/04 08:29	2014/07/04 11:15	21		19		262		213	
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	22		29		279		192	

Program Name: L080102_01.sas / Output: l080102_01_b.rtf
Date of Table Generation: 2015-02-17 21:04
Data Source: adlbbe

Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.2

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	AST(GOT) (IU/L) mesure-ment	AST(GOT) (IU/L) Abnormal / Abnormal change	ALT(GPT) (IU/L) mesure-ment	ALT(GPT) (IU/L) Abnormal / Abnormal change	ALP (IU/L) mesure-ment	ALP (IU/L) Abnormal / Abnormal change	LDH (IU/L) mesure-ment	LDH (IU/L) Abnormal / Abnormal change
KN-07-01, with co-administration of L-arginine											
0 wks	2013/10/31 11:55	-	2013/10/31 13:35	14		16		166		180	
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	12	yes	9		167		207	
12 wks	2014/01/24 07:00	2014/01/24 07:00	2014/01/24 11:47	14		11		197		211	
24 wks	2014/04/18 09:00	2014/04/17 20:00	2014/04/18 14:10	16		12		208		216	
36 wks	2014/07/18 07:00	2014/07/18 07:00	2014/07/18 11:02	13		10		190		208	
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	12	yes	10		183		186	
KN-08-01, with co-administration of L-arginine											
0 wks	2013/10/28 12:10	-	2013/10/28 13:40	20		10		303		133	
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	19		8		294		168	
12 wks	2014/01/22 07:40	2014/01/22 08:15	2014/01/22 10:30	18		8		358	yes	149	
unscheduled test	2014/03/18 18:00	2014/03/18 18:20	2014/03/19 06:00	18		7		334		203	
unscheduled test	2014/03/23 18:00	2014/03/23 18:15	2014/03/24 06:00	23		6		264		183	
24 wks	2014/04/16 07:40	2014/04/16 08:15	2014/04/16 10:50	21		7		284		183	
36 wks	2014/07/09 07:40	2014/07/09 08:25	2014/07/09 10:40	18		8		344	yes	140	
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	19		8		339	yes	144	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.2

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	AST(GOT) (IU/L) mesure-ment	AST(GOT) (IU/L) Abnormal / Abnormal change	ALT(GPT) (IU/L) mesure-ment	ALT(GPT) (IU/L) Abnormal / Abnormal change	ALP (IU/L) mesure-ment	ALP (IU/L) Abnormal / Abnormal change	LDH (IU/L) mesure-ment	LDH (IU/L) Abnormal / Abnormal change
KN-10-01, with co-administration of L-arginine											
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	53	yes	34	yes	601	yes	420	yes
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	48	yes	32	yes	527	yes	345	yes
12 wks	2014/01/29 13:10	2014/01/29 13:30	2014/01/29 14:45	29		24		595	yes	295	yes
24 wks	2014/04/23 12:15	2014/04/23 12:45	2014/04/23 14:35	79	yes	54	yes	498	yes	583	yes
36 wks	2014/07/23 12:00	2014/07/23 12:50	2014/07/23 14:20	39	yes	29		450	yes	297	yes
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	49	yes	28		358		320	yes
KN-11-01, with co-administration of L-arginine											
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	18		19		435	yes	179	
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	21		24		512	yes	179	
12 wks	2014/02/25 08:00	2014/02/25 08:30	2014/02/25 10:30	19		20		596	yes	165	
24 wks	2014/05/26 07:30	2014/05/26 07:45	2014/05/26 10:40	21		21		556	yes	166	
36 wks	2014/08/18 07:10	2014/08/18 07:22	2014/08/18 10:50	21		27		408	yes	154	
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	18		18		365	yes	166	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.2

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	AST(GOT) (IU/L) mesure-ment	AST(GOT) (IU/L) Abnormal / Abnormal change	ALT(GPT) (IU/L) mesure-ment	ALT(GPT) (IU/L) Abnormal / Abnormal change	ALP (IU/L) mesure-ment	ALP (IU/L) Abnormal / Abnormal change	LDH (IU/L) mesure-ment	LDH (IU/L) Abnormal / Abnormal change
KN-12-01, with co-administration of L-arginine											
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	21		16		180		206	
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	20		12		192		203	
12 wks	2014/02/10 07:00	2014/02/10 08:00	2014/02/10 11:50	20		9		221		201	
24 wks	2014/04/27 18:30	2014/04/28 10:00	2014/04/28 12:00	15		10		244		192	
36 wks	2014/07/27 18:30	2014/07/28 08:30	2014/07/28 11:50	24		12		251		213	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	30		13		192		244	yes
KN-13-01, with co-administration of L-arginine											
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	15		21		291		162	
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	14		24		350		154	
unscheduled test	2014/02/10 12:30	2014/02/10 13:00	2014/02/10 14:22	19		23		367	yes	186	
12 wks	2014/03/14 12:30	2014/03/14 13:30	2014/03/14 13:53	16		21		390	yes	186	
24 wks	2014/05/30 11:30	2014/05/30 12:00	2014/05/30 13:48	18		20		362	yes	181	
36 wks	2014/08/22 12:00	2014/08/22 12:00	2014/08/22 12:38	16		22		366	yes	163	
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:11	14		20		336		167	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.3

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	γ-GTP (IU/L) mesure-ment	γ-GTP (IU/L) Abnormal / Abnormal change	CK (U/L) mesure-ment	CK (U/L) Abnormal / Abnormal change	T-Bil (mg/dL) mesure-ment	T-Bil (mg/dL) Abnormal / Abnormal change	D-Bil (mg/dL) mesure-ment	D-Bil (mg/dL) Abnormal / Abnormal change
KN-01-01, with co-administration of L-arginine											
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	13		146		0.2	yes	0.05	yes
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	13		163		0.2	yes	0.06	
12 wks	2013/12/26 08:30	2013/12/26 07:15	2013/12/26 09:30	15		117		0.2	yes	0.04	yes
24 wks	2014/03/20 06:50	2014/03/20 07:10	2014/03/20 09:10	19		127		0.2	yes	0.06	
36 wks	2014/06/12 06:45	2014/06/12 07:05	2014/06/12 08:40	18		115		0.2	yes	0.05	yes
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	23		166		0.2	yes	0.06	
KN-03-01, with co-administration of L-arginine											
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	73	yes	147		0.3		0.1	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	83	yes	160		0.4		0.1	
12 wks	2014/03/31 08:00	2014/03/31 08:40	2014/03/31 09:51	81	yes	201	yes	0.4		0.1	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	68		561	yes	0.3			
24 wks	2014/06/09 08:00	2014/06/09 08:15	2014/06/09 09:30	53		88		0.5		0.2	
36 wks	2014/09/01 07:50	2014/09/01 08:10	2014/09/01 10:00	87	yes	100		0.5		0.1	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	105	yes	146		0.4		0.1	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.3

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	γ-GTP (IU/L) mesure-ment	γ-GTP (IU/L) Abnormal / Abnormal change	CK (U/L) mesure-ment	CK (U/L) Abnormal / Abnormal change	T-Bil (mg/dL) mesure-ment	T-Bil (mg/dL) Abnormal / Abnormal change	D-Bil (mg/dL) mesure-ment	D-Bil (mg/dL) Abnormal / Abnormal change
KN-04-01, without co-administration of L-arginine											
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	12		54	yes	1.3	yes	0.3	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	14		74		0.8		0.2	
12 wks	2014/02/06 12:30	2014/02/06 12:30	2014/02/06 13:40	16		80		1.1		0.2	
24 wks	2014/05/09 11:30	2014/05/09 11:45	2014/05/09 14:58	16		54	yes	1.3	yes	0.3	
36 wks	2014/07/18 12:30	2014/07/18 12:40	2014/07/18 14:15	15		74		0.9		0.2	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	16		86		0.8		0.2	
KN-05-01, with co-administration of L-arginine											
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	19		299	yes	0.6		0.1	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	19		321	yes	0.7		0.1	
12 wks	2014/01/24 08:20	2014/01/24 08:30	2014/01/24 10:49	16		255		0.6		0.1	
24 wks	2014/04/18 07:30	2014/04/18 07:50	2014/04/18 10:14	17		189		0.7		0.2	
36 wks	2014/07/04 08:20	2014/07/04 08:29	2014/07/04 11:15	17		259		1.1		0.2	
unscheduled test	-	-	2014/08/06 18:26			1435	yes	yes			
unscheduled test	-	-	2014/10/29 16:07			195					
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	17		112		1		0.1	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.3

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	γ-GTP (IU/L) mesure-ment	γ-GTP (IU/L) Abnormal / Abnormal change	CK (U/L) mesure-ment	CK (U/L) Abnormal / Abnormal change	T-Bil (mg/dL) mesure-ment	T-Bil (mg/dL) Abnormal / Abnormal change	D-Bil (mg/dL) mesure-ment	D-Bil (mg/dL) Abnormal / Abnormal change
KN-07-01, with co-administration of L-arginine											
0 wks	2013/10/31 11:55	-	2013/10/31 13:35	15		63		0.2	yes	0.1	
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	14		84		0.4		0	
12 wks	2014/01/24 07:00	2014/01/24 07:00	2014/01/24 11:47	16		104		0.5		0	
24 wks	2014/04/18 09:00	2014/04/17 20:00	2014/04/18 14:10	15		76		0.5		0	
36 wks	2014/07/18 07:00	2014/07/18 07:00	2014/07/18 11:02	14		108		0.3		0	
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	13		88		0.4		0	
KN-08-01, with co-administration of L-arginine											
0 wks	2013/10/28 12:10	-	2013/10/28 13:40	60		77		0.3		0.1	
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	62		93		0.4		0.1	
12 wks	2014/01/22 07:40	2014/01/22 08:15	2014/01/22 10:30	74	yes	72		0.4		0.1	
unscheduled test	2014/03/18 18:00	2014/03/18 18:20	2014/03/19 06:00	85	yes	81		0.7			
unscheduled test	2014/03/23 18:00	2014/03/23 18:15	2014/03/24 06:00	76	yes	116		0.3			
24 wks	2014/04/16 07:40	2014/04/16 08:15	2014/04/16 10:50	58		94		0.4		0.1	
36 wks	2014/07/09 07:40	2014/07/09 08:25	2014/07/09 10:40	87	yes	63		0.4		0.2	
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	97	yes	164		0.4		0.1	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.3

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	γ-GTP (IU/L) mesure-ment	γ-GTP Abnormal / Abnormal change	CK (U/L) mesure-ment	CK Abnormal / Abnormal change	T-Bil (mg/dL) mesure-ment	T-Bil Abnormal / Abnormal change	D-Bil (mg/dL) mesure-ment	D-Bil Abnormal / Abnormal change
KN-10-01, with co-administration of L-arginine											
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	96	yes	643	yes	0.4		0	
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	124	yes	391	yes	0.4		0	
12 wks	2014/01/29 13:10	2014/01/29 13:30	2014/01/29 14:45	104	yes	307	yes	0.4		0.1	
24 wks	2014/04/23 12:15	2014/04/23 12:45	2014/04/23 14:35	102	yes	3264	yes yes	0.4		0.1	
36 wks	2014/07/23 12:00	2014/07/23 12:50	2014/07/23 14:20	134	yes	350	yes	0.4		0.1	
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	152	yes yes	883	yes yes	0.4		0.1	
KN-11-01, with co-administration of L-arginine											
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	56	yes	139		0.23	yes	0.05	
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	60	yes	166		0.26	yes	0.05	
12 wks	2014/02/25 08:00	2014/02/25 08:30	2014/02/25 10:30	49	yes	180		0.33		0.05	
24 wks	2014/05/26 07:30	2014/05/26 07:45	2014/05/26 10:40	51	yes	314	yes	0.33		0.05	
36 wks	2014/08/18 07:10	2014/08/18 07:22	2014/08/18 10:50	58	yes	168		0.33		0.05	
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	54	yes	162		0.25	yes	0.05	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.3

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	γ-GTP (IU/L) mesur-ement	γ-GTP Abnormal / Abnormal change	CK (U/L) mesure-ment	CK Abnormal / Abnormal change	T-Bil (mg/dL) mesure-ment	T-Bil Abnormal / Abnormal change	D-Bil (mg/dL) mesure-ment	D-Bil Abnormal / Abnormal change
KN-12-01, with co-administration of L-arginine											
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	27		118		0.5		0.1	
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	26		122		0.5		0.1	
12 wks	2014/02/10 07:00	2014/02/10 08:00	2014/02/10 11:50	20		137		0.5		0	
24 wks	2014/04/27 18:30	2014/04/28 10:00	2014/04/28 12:00	20		73		0.7		0.1	
36 wks	2014/07/27 18:30	2014/07/28 08:30	2014/07/28 11:50	22		169	yes	0.6		0.1	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	22		192	yes	0.6		0.1	
KN-13-01, with co-administration of L-arginine											
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	60		78		0.5		0.1	
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	74		72		0.3		0.1	
unscheduled test	2014/02/10 12:30	2014/02/10 13:00	2014/02/10 14:22	89	yes	119		0.4		0.1	
12 wks	2014/03/14 12:30	2014/03/14 13:30	2014/03/14 13:53	70		138		0.3		0.1	
24 wks	2014/05/30 11:30	2014/05/30 12:00	2014/05/30 13:48	80	yes	196		0.3		0	
36 wks	2014/08/22 12:00	2014/08/22 12:00	2014/08/22 12:38	98	yes yes	92		0.3		0.1	
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:11	91	yes yes	92		0.3		0.1	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.4

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	BUN (mg/dL) mesure-ment	BUN (mg/dL) Abnormal / Abnormal change	Cre (mg/dL) mesure-ment	Cre (mg/dL) Abnormal / Abnormal change	eGFR (mL/min/1.73 m^2) mesurement	Uric acid (mg/dL) mesure-ment	Uric acid (mg/dL) Abnormal / Abnormal change
KN-01-01, with co-administration of L-arginine										
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	15		0.21	yes	263.5	3.2	
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	21		0.16	yes	354.8	3.5	
12 wks	2013/12/26 08:30	2013/12/26 07:15	2013/12/26 09:30	18		0.18	yes	311.9	2.7	
24 wks	2014/03/20 06:50	2014/03/20 07:10	2014/03/20 09:10	24	yes	0.17	yes	332	2.9	
36 wks	2014/06/12 06:45	2014/06/12 07:05	2014/06/12 08:40	18		0.19	yes	294	2.8	
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	22		0.11	yes	534.5	2.9	
KN-03-01, with co-administration of L-arginine										
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	17		0.6	yes	137.9	5.2	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	17		0.5	yes	168.4	3.6	
12 wks	2014/03/31 08:00	2014/03/31 08:40	2014/03/31 09:51	14		0.53	yes	158	3.6	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	14		0.48	yes	176.1		
24 wks	2014/06/09 08:00	2014/06/09 08:15	2014/06/09 09:30	11		0.47	yes	180.2	2.4	yes
36 wks	2014/09/01 07:50	2014/09/01 08:10	2014/09/01 10:00	15		0.46	yes	184.5	2.8	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	13		0.52	yes	161.3	2.9	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.4

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	BUN (mg/dL) mesure-ment	BUN (mg/dL) Abnormal / Abnormal change	Cre (mg/dL) mesure-ment	Cre (mg/dL) Abnormal / Abnormal change	eGFR (mL/min/1.73 m^2) mesurement	Uric acid (mg/dL) mesure-ment	Uric acid (mg/dL) Abnormal / Abnormal change
KN-04-01, without co-administration of L-arginine										
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	14		0.83		88.8	5.1	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	11		0.74		100.7	4.1	
12 wks	2014/02/06 12:30	2014/02/06 12:30	2014/02/06 13:40	8		0.76		97.8	3.3	
24 wks	2014/05/09 11:30	2014/05/09 11:45	2014/05/09 14:58	12		0.75		99.2	3.8	
36 wks	2014/07/18 12:30	2014/07/18 12:40	2014/07/18 14:15	11		0.84		87.6	3.8	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	11		0.73		102.2	3.8	
KN-05-01, with co-administration of L-arginine										
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	20.8		0.65		133.5	4.6	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	25.2	yes	0.64		135.8	3.8	
12 wks	2014/01/24 08:20	2014/01/24 08:30	2014/01/24 10:49	28.7	yes	0.68		127.1	3.7	
24 wks	2014/04/18 07:30	2014/04/18 07:50	2014/04/18 10:14	25.7	yes	0.68		127.1	3.4	yes
36 wks	2014/07/04 08:20	2014/07/04 08:29	2014/07/04 11:15	23.5	yes	0.62		140.6	3.6	
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	20.3		0.73		117.6	3.5	yes

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.4

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	BUN (mg/dL) mesure-ment	BUN Abnormal / Abnormal change	Cre (mg/dL) mesure-ment	Cre Abnormal / Abnormal change	eGFR (mL/min/1.73 m^2) mesurement	Uric acid (mg/dL) mesure-ment	Uric acid Abnormal / Abnormal change
KN-07-01, with co-administration of L-arginine										
0 wks	2013/10/31 11:55	-	2013/10/31 13:35	19		0.63		89.5	4.3	
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	19		0.72	yes	77.4	4	
12 wks	2014/01/24 07:00	2014/01/24 07:00	2014/01/24 11:47	19		0.68		82.4	4.2	
24 wks	2014/04/18 09:00	2014/04/17 20:00	2014/04/18 14:10	18		0.61		92.8	4.2	
36 wks	2014/07/18 07:00	2014/07/18 07:00	2014/07/18 11:02	21		0.75	yes	74	3.4	
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	20		1	yes	54	4.5	
KN-08-01, with co-administration of L-arginine										
0 wks	2013/10/28 12:10	-	2013/10/28 13:40	18.4		0.72		93.2	4	
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	18.2		0.59	yes	115.9	2.8	yes
12 wks	2014/01/22 07:40	2014/01/22 08:15	2014/01/22 10:30	19		0.66		102.5	3	yes
unscheduled test	2014/03/18 18:00	2014/03/18 18:20	2014/03/19 06:00	17.7		0.61		111.7		
unscheduled test	2014/03/23 18:00	2014/03/23 18:15	2014/03/24 06:00	14.8		0.61		111.7		
24 wks	2014/04/16 07:40	2014/04/16 08:15	2014/04/16 10:50	17.5		0.54	yes	127.7	2.8	yes
36 wks	2014/07/09 07:40	2014/07/09 08:25	2014/07/09 10:40	21.4	yes	0.65		104.2	2.9	yes
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	21.5	yes	0.61		111.7	2.3	yes

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Data Source: adlbbe

Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.4

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	BUN (mg/dL) mesure-ment	BUN (mg/dL) Abnormal / Abnormal change	Cre (mg/dL) mesure-ment	Cre (mg/dL) Abnormal / Abnormal change	eGFR (mL/min/1.73 m^2) mesurement	Uric acid (mg/dL) mesure-ment	Uric acid (mg/dL) Abnormal / Abnormal change
KN-10-01, with co-administration of L-arginine										
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	14		0.4	yes	243	5.9	
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	15		0.4	yes	243	5	
12 wks	2014/01/29 13:10	2014/01/29 13:30	2014/01/29 14:45	16		0.3	yes	332.9	4.7	
24 wks	2014/04/23 12:15	2014/04/23 12:45	2014/04/23 14:35	15		0.4	yes	243	5.7	
36 wks	2014/07/23 12:00	2014/07/23 12:50	2014/07/23 14:20	14		0.4	yes	243	4.2	
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	14		0.4	yes	243	3.6	
KN-11-01, with co-administration of L-arginine										
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	14.3		0.39	yes	254.8	5.2	
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	15.4		0.37	yes	269.9	5.59	
12 wks	2014/02/25 08:00	2014/02/25 08:30	2014/02/25 10:30	14.2		0.38	yes	262.2	5.31	
24 wks	2014/05/26 07:30	2014/05/26 07:45	2014/05/26 10:40	16.2		0.38	yes	262.2	4.95	
36 wks	2014/08/18 07:10	2014/08/18 07:22	2014/08/18 10:50	14.1		0.33	yes	305.9	4.43	
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	15.7		0.39	yes	254.8	4.85	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.4

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	BUN (mg/dL) mesure-ment	BUN (mg/dL) Abnormal / Abnormal change	Cre (mg/dL) mesure-ment	Cre (mg/dL) Abnormal / Abnormal change	eGFR (mL/min/1.73 m^2) mesurement	Uric acid (mg/dL) mesure-ment	Uric acid (mg/dL) Abnormal / Abnormal change
KN-12-01, with co-administration of L-arginine										
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	8		0.41		143.3	3.4	
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	7	yes	0.38	yes	155.7	3	
12 wks	2014/02/10 07:00	2014/02/10 08:00	2014/02/10 11:50	7	yes	0.41		143.3	2.5	
24 wks	2014/04/27 18:30	2014/04/28 10:00	2014/04/28 12:00	8		0.37	yes	160.3	1.9	yes
36 wks	2014/07/27 18:30	2014/07/28 08:30	2014/07/28 11:50	10		0.39	yes	151.3	2.7	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	13		0.39	yes	151.3	2.6	
KN-13-01, with co-administration of L-arginine										
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	17.7		0.57	yes	126.3	4	
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	24.1	yes	0.49	yes	149	2.8	yes
unscheduled test	2014/02/10 12:30	2014/02/10 13:00	2014/02/10 14:22	24.3	yes	0.5	yes	145.8	3.7	
12 wks	2014/03/14 12:30	2014/03/14 13:30	2014/03/14 13:53	25.8	yes	0.53	yes	136.8	3.1	yes
24 wks	2014/05/30 11:30	2014/05/30 12:00	2014/05/30 13:48	23.9	yes	0.59	yes	121.6	3.7	
36 wks	2014/08/22 12:00	2014/08/22 12:00	2014/08/22 12:38	24.8	yes	0.57	yes	126.3	3.8	
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:11	25.3	yes	0.54	yes	134	3.7	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.5

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	TG (ng/mL) mesure-ment	TG Abnormal / Abnormal change	T-Cho (mg/dL) mesure-ment	T-Cho Abnormal / Abnormal change	Na (mEq/L) mesure-ment	Na Abnormal / Abnormal change	K (mEq/L) mesure-ment	K Abnormal / Abnormal change
KN-01-01, with co-administration of L-arginine											
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	270	yes	196		140		3.9	
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	194	yes	188		139		4.2	
12 wks	2013/12/26 08:30	2013/12/26 07:15	2013/12/26 09:30	232	yes	177		139		4.4	
24 wks	2014/03/20 06:50	2014/03/20 07:10	2014/03/20 09:10	159	yes	209		143		3.9	
36 wks	2014/06/12 06:45	2014/06/12 07:05	2014/06/12 08:40	275	yes	201		142		3.8	
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	138		219		140		4.3	
KN-03-01, with co-administration of L-arginine											
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	97		142		144		4	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	85		168		144		3.8	
12 wks	2014/03/31 08:00	2014/03/31 08:40	2014/03/31 09:51	56		160		142		3.9	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	73		157		142		3.9	
24 wks	2014/06/09 08:00	2014/06/09 08:15	2014/06/09 09:30	75		178		142		3.3	yes
36 wks	2014/09/01 07:50	2014/09/01 08:10	2014/09/01 10:00	71		155		143		3.7	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	104		153		142		3.8	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.5

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	TG (ng/mL) mesure-ment	TG Abnormal / Abnormal change	T-Cho (mg/dL) mesure-ment	T-Cho Abnormal / Abnormal change	Na (mEq/L) mesure-ment	Na Abnormal / Abnormal change	K (mEq/L) mesure-ment	K Abnormal / Abnormal change
KN-04-01, without co-administration of L-arginine											
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	97		148		145		4	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	147		153		142		4.2	
12 wks	2014/02/06 12:30	2014/02/06 12:30	2014/02/06 13:40	232	yes	140		141		3.9	
24 wks	2014/05/09 11:30	2014/05/09 11:45	2014/05/09 14:58	150		152		141		4.2	
36 wks	2014/07/18 12:30	2014/07/18 12:40	2014/07/18 14:15	349	yes	149		142		4	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	126		129	yes	143		3.9	
KN-05-01, with co-administration of L-arginine											
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	365	yes	188		140		3.9	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	316	yes	193		141		4.1	
12 wks	2014/01/24 08:20	2014/01/24 08:30	2014/01/24 10:49	211	yes	190		142		4.3	
24 wks	2014/04/18 07:30	2014/04/18 07:50	2014/04/18 10:14	230	yes	194		142		4.3	
36 wks	2014/07/04 08:20	2014/07/04 08:29	2014/07/04 11:15	281	yes	194		141		4.4	
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	149		143		143		3.6	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.5

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	TG (ng/mL) mesure-ment	TG Abnormal / Abnormal change	T-Cho (mg/dL) mesure-ment	T-Cho Abnormal / Abnormal change	Na (mEq/L) mesure-ment	Na Abnormal / Abnormal change	K (mEq/L) mesure-ment	K Abnormal / Abnormal change	
KN-07-01, with co-administration of L-arginine												
0 wks	2013/10/31 11:55	-	2013/10/31 13:35	327	yes	142		137	yes	4		
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	134		170		138		5.1	yes	
12 wks	2014/01/24 07:00	2014/01/24 07:00	2014/01/24 11:47	99		183		138		5.7	yes	yes
unscheduled test	-	-	2014/03/14 09:00					139		5.3	yes	yes
24 wks	2014/04/18 09:00	2014/04/17 20:00	2014/04/18 14:10	59		167		140		4.7		
36 wks	2014/07/18 07:00	2014/07/18 07:00	2014/07/18 11:02	125		181		137	yes	4.3		
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	126		172		140		4.1		
KN-08-01, with co-administration of L-arginine												
0 wks	2013/10/28 12:10	-	2013/10/28 13:40	90		151		142		3.9		
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	63		151		141		4.1		
12 wks	2014/01/22 07:40	2014/01/22 08:15	2014/01/22 10:30	76		149		141		4.2		
unscheduled test	2014/03/18 18:00	2014/03/18 18:20	2014/03/19 06:00					138		3.9		
unscheduled test	2014/03/23 18:00	2014/03/23 18:15	2014/03/24 06:00					141		4.5		
24 wks	2014/04/16 07:40	2014/04/16 08:15	2014/04/16 10:50	47	yes	150		142		4.1		
36 wks	2014/07/09 07:40	2014/07/09 08:25	2014/07/09 10:40	67		148		142		4.2		
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	46	yes	153		143		4.2		

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.5

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	TG (ng/mL) mesure-ment	TG Abnormal / Abnormal change	T-Cho (mg/dL) mesure-ment	T-Cho Abnormal / Abnormal change	Na (mEq/L) mesure-ment	Na Abnormal / Abnormal change	K (mEq/L) mesure-ment	K Abnormal / Abnormal change
KN-10-01, with co-administration of L-arginine											
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	429	yes	280	yes	138		4.5	
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	630	yes	298	yes	142		4.7	
12 wks	2014/01/29 13:10	2014/01/29 13:30	2014/01/29 14:45	969	yes yes	251	yes	140		4.2	
24 wks	2014/04/23 12:15	2014/04/23 12:45	2014/04/23 14:35	293	yes	257	yes	142		3.7	
36 wks	2014/07/23 12:00	2014/07/23 12:50	2014/07/23 14:20	508	yes	262	yes	141		3.8	
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	163	yes	177		136	yes	4.4	
KN-11-01, with co-administration of L-arginine											
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	125		115	yes	134	yes	5.2	yes
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	114		131		140		4.5	
12 wks	2014/02/25 08:00	2014/02/25 08:30	2014/02/25 10:30	100		114	yes	134	yes	4.7	
24 wks	2014/05/26 07:30	2014/05/26 07:45	2014/05/26 10:40	85		118	yes	130	yes	4.8	
36 wks	2014/08/18 07:10	2014/08/18 07:22	2014/08/18 10:50	98		116	yes	129	yes	4.4	
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	104		120	yes	137	yes	4.3	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.5

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	TG (ng/mL) mesure-ment	TG Abnormal / Abnormal change	T-Cho (mg/dL) mesure-ment	T-Cho Abnormal / Abnormal change	Na (mEq/L) mesure-ment	Na Abnormal / Abnormal change	K (mEq/L) mesure-ment	K Abnormal / Abnormal change
KN-12-01, with co-administration of L-arginine											
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	103		264	yes	132	yes	4	
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	116		276	yes	133	yes	3.9	
12 wks	2014/02/10 07:00	2014/02/10 08:00	2014/02/10 11:50	104		276	yes	126	yes	4	
24 wks	2014/04/27 18:30	2014/04/28 10:00	2014/04/28 12:00	114		234		131	yes	4.2	
36 wks	2014/07/27 18:30	2014/07/28 08:30	2014/07/28 11:50	94		279	yes	133	yes	3.8	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	109		304	yes	132	yes	3.9	
KN-13-01, with co-administration of L-arginine											
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	424	yes	224	yes	138		4.2	
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	467	yes	209		139		4.2	
unscheduled test	2014/02/10 12:30	2014/02/10 13:00	2014/02/10 14:22	275	yes	214		138		4.5	
12 wks	2014/03/14 12:30	2014/03/14 13:30	2014/03/14 13:53	410	yes	216		138		4.3	
24 wks	2014/05/30 11:30	2014/05/30 12:00	2014/05/30 13:48	389	yes	216		142		4.3	
36 wks	2014/08/22 12:00	2014/08/22 12:00	2014/08/22 12:38	522	yes	226	yes	138		4.7	
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:11	320	yes	218		140		4.5	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.6

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/					
				Cl (mEq/L)	
weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	measurement	Abnormal / Abnormal change
KN-01-01, with co-administration of L-arginine					
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	103	
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	103	
12 wks	2013/12/26 08:30	2013/12/26 07:15	2013/12/26 09:30	106	
24 wks	2014/03/20 06:50	2014/03/20 07:10	2014/03/20 09:10	105	
36 wks	2014/06/12 06:45	2014/06/12 07:05	2014/06/12 08:40	102	
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	102	
KN-03-01, with co-administration of L-arginine					
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	103	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	104	
12 wks	2014/03/31 08:00	2014/03/31 08:40	2014/03/31 09:51	102	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	104	
24 wks	2014/06/09 08:00	2014/06/09 08:15	2014/06/09 09:30	104	
36 wks	2014/09/01 07:50	2014/09/01 08:10	2014/09/01 10:00	103	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	103	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.6

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/					
				Cl (mEq/L)	
weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	mesurement	Abnormal / Abnormal change
KN-04-01, without co-administration of L-arginine					
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	105	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	104	
12 wks	2014/02/06 12:30	2014/02/06 12:30	2014/02/06 13:40	103	
24 wks	2014/05/09 11:30	2014/05/09 11:45	2014/05/09 14:58	105	
36 wks	2014/07/18 12:30	2014/07/18 12:40	2014/07/18 14:15	104	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	106	
KN-05-01, with co-administration of L-arginine					
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	103	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	104	
12 wks	2014/01/24 08:20	2014/01/24 08:30	2014/01/24 10:49	104	
24 wks	2014/04/18 07:30	2014/04/18 07:50	2014/04/18 10:14	105	
36 wks	2014/07/04 08:20	2014/07/04 08:29	2014/07/04 11:15	106	
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	108	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.6

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Cl (mEq/L) mesurement	Cl (mEq/L) Abnormal / Abnormal change
KN-07-01, with co-administration of L-arginine					
0 wks	2013/10/31 11:55	-	2013/10/31 13:35	101	
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	101	
12 wks	2014/01/24 07:00	2014/01/24 07:00	2014/01/24 11:47	100	
unscheduled test	-	-	2014/03/14 09:00	100	
24 wks	2014/04/18 09:00	2014/04/17 20:00	2014/04/18 14:10	100	
36 wks	2014/07/18 07:00	2014/07/18 07:00	2014/07/18 11:02	102	
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	102	
KN-08-01, with co-administration of L-arginine					
0 wks	2013/10/28 12:10	-	2013/10/28 13:40	107	
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	107	
12 wks	2014/01/22 07:40	2014/01/22 08:15	2014/01/22 10:30	106	
unscheduled test	2014/03/18 18:00	2014/03/18 18:20	2014/03/19 06:00	102	
unscheduled test	2014/03/23 18:00	2014/03/23 18:15	2014/03/24 06:00	106	
24 wks	2014/04/16 07:40	2014/04/16 08:15	2014/04/16 10:50	108	
36 wks	2014/07/09 07:40	2014/07/09 08:25	2014/07/09 10:40	104	
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	106	

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.6

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/					
				Cl (mEq/L)	
weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	mesurement	Abnormal / Abnormal change
KN-10-01, with co-administration of L-arginine					
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	101	
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	104	
12 wks	2014/01/29 13:10	2014/01/29 13:30	2014/01/29 14:45	102	
24 wks	2014/04/23 12:15	2014/04/23 12:45	2014/04/23 14:35	103	
36 wks	2014/07/23 12:00	2014/07/23 12:50	2014/07/23 14:20	100	
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	98	yes
KN-11-01, with co-administration of L-arginine					
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	97	yes
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	102	
12 wks	2014/02/25 08:00	2014/02/25 08:30	2014/02/25 10:30	97	yes
24 wks	2014/05/26 07:30	2014/05/26 07:45	2014/05/26 10:40	94	yes
36 wks	2014/08/18 07:10	2014/08/18 07:22	2014/08/18 10:50	92	yes
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	97	yes

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Table 4.3.4-4 List of biochemical examinations (Safety Analysis) No.6

Subject individual number, without co-administration of L-arginine・with co-administration of L-arginine/					
				Cl (mEq/L)	
weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	mesurement	Abnormal / Abnormal change
KN-12-01, with co-administration of L-arginine					
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	92	yes
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	93	yes
12 wks	2014/02/10 07:00	2014/02/10 08:00	2014/02/10 11:50	90	yes
24 wks	2014/04/27 18:30	2014/04/28 10:00	2014/04/28 12:00	94	yes
36 wks	2014/07/27 18:30	2014/07/28 08:30	2014/07/28 11:50	91	yes
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	94	yes
KN-13-01, with co-administration of L-arginine					
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	102	
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	102	
unscheduled test	2014/02/10 12:30	2014/02/10 13:00	2014/02/10 14:22	100	
12 wks	2014/03/14 12:30	2014/03/14 13:30	2014/03/14 13:53	101	
24 wks	2014/05/30 11:30	2014/05/30 12:00	2014/05/30 13:48	104	
36 wks	2014/08/22 12:00	2014/08/22 12:00	2014/08/22 12:38	103	
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:11	103	

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Data Source: adlbbe

Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.1

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Taurine (nmol/mL) mesure-ment	Taurine (nmol/mL) ab-normal	Aspartate (nmol/mL) mesure-ment	Aspartate (nmol/mL) ab-normal	Hydroxyproline (nmol/mL) mesure-ment	Hydroxyproline (nmol/mL) ab-normal	Threonine (nmol/mL) mesure-ment	Threonine (nmol/mL) ab-normal	Serine (nmol/mL) mesure-ment	Serine (nmol/mL) ab-normal	Asparagine (nmol/mL) mesure-ment	Asparagine (nmol/mL) ab-normal
KN-01-01, with co-administration of L-arginine															
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	70.3		2		TR		46.9	yes	61.3	yes	39.6	yes
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	1123	yes	3	yes	TR		47.1	yes	52.7	yes	31	yes
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	1172	yes	3.5	yes	TR		70.5		57.9	yes	38.3	yes
KN-03-01, with co-administration of L-arginine															
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	35.4	yes	2.8	yes	TR		90.3		113.1		40.5	yes
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	1106.5	yes	3.7	yes	TR		108.4		133.7		40.9	yes
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	665.2	yes	2		TR		91		117.8		35.7	yes
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	1578.7	yes	2.2		10.3		96.2		120.4		35.7	yes
KN-04-01, without co-administration of L-arginine															
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	57.4		2.2		11.7		157.3		161.6		61.2	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	1671	yes	2.6	yes	10.4		112.7		138.5		55.3	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	1168.5	yes	TR		15.1		118.1		142.8		55.7	
KN-05-01, with co-administration of L-arginine															
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	57.9		2.9	yes	11.2		72.6		90.4		38.1	yes
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	925.5	yes	TR	yes	TR	yes	63.9	yes	78		37	yes
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	188.9	yes	TR		TR		89.7		121		48.4	

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.1

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Taurine (nmol/mL) mesure-ment	Taurine (nmol/mL) ab-normal	Aspartate (nmol/mL) mesure-ment	Aspartate (nmol/mL) ab-normal	Hydroxyproline (nmol/mL) mesure-ment	Hydroxyproline (nmol/mL) ab-normal	Threonine (nmol/mL) mesure-ment	Threonine (nmol/mL) ab-normal	Serine (nmol/mL) mesure-ment	Serine (nmol/mL) ab-normal	Asparagine (nmol/mL) mesure ment	Asparagine (nmol/mL) ab-normal
KN-07-01, with co-administration of L-arginine															
0 wks	2013/10/31 11:55	-	2013/10/31 10:35	45.5		3.6	yes	TR		51	yes	74.1		25.8	yes
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	1791.5	yes	3.5	yes	TR		40.8	yes	50.3	yes	22.6	yes
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	537.3	yes	2.1		15.4		65.3	yes	77.9		41.6	yes
KN-08-01, with co-administration of L-arginine															
0 wks	-	-	2013/10/28 11:50	63.2		TR		12.4		76.1		96		39.3	yes
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	923	yes	2.6	yes	14		70.5		97.6		40.8	yes
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	832	yes	TR		TR		61.9	yes	82.7		41	yes
KN-10-01, with co-administration of L-arginine															
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	102.2	yes	4.5	yes	17.6		105.3		134.9		44.6	yes
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	704.1	yes	4.9	yes	TR		71.4		94.7		31.8	yes
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	1229	yes	6.6	yes	ND		39.9	yes	72.1	yes	19.7	yes

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.1

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Taurine (nmol/mL) mesure-ment	Taurine (nmol/mL) ab-normal	Aspartate (nmol/mL) mesure-ment	Aspartate (nmol/mL) ab-normal	Hydroxyproline (nmol/mL) mesure-ment	Hydroxyproline (nmol/mL) ab-normal	Threonine (nmol/mL) mesure-ment	Threonine (nmol/mL) ab-normal	Serine (nmol/mL) mesure-ment	Serine (nmol/mL) ab-normal	Asparagine (nmol/mL) mesure-ment	Asparagine (nmol/mL) ab-normal
KN-11-01, with co-administration of L-arginine															
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	52.2		2.7	yes	20.4		101.5		142.6		41.8	yes
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	797.7	yes	2.5	yes	16.4		86.5		122.4		30.7	yes
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	606.7	yes	2.3		20.2		95.4		127.9		30.6	yes
KN-12-01, with co-administration of L-arginine															
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	28.8	yes	TR		TR		58	yes	74.6		33.8	yes
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	935.9	yes	2.8	yes	10.5		87.6		98.8		46.1	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	1115.5	yes	TR		TR		66.3	yes	79.4		34.1	yes
KN-13-01, with co-administration of L-arginine															
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	62.8		3	yes	TR		60.1	yes	69.6	yes	38	yes
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	889.1	yes	3.2	yes	15.3		48.4	yes	58.4	yes	31.6	yes
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:05	1028.1	yes	5.1	yes	TR		43.2	yes	64.8	yes	26.6	yes

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.2

Subject individual number, without・with co-administration of L-arginine/

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Glutamate (nmol/mL)		Glutamine (nmol/mL)		Sarcosine (nmol/mL)		α-aminoadipic acid (nmol/mL)		Proline (nmol/mL)		Glycine (nmol/mL)	
				mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal
KN-01-01, with co-administration of L-arginine															
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	19.7		346.6	yes	ND	yes	ND		86.5		113	yes
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	42		304.3	yes	ND	yes	ND		139.8		111	yes
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	52.5		369.5	yes	ND	yes	ND		182		115.4	yes
KN-03-01, with co-administration of L-arginine															
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	29.2		578		ND	yes	ND		151.2		165.3	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	74.7	yes	475.3		ND	yes	TR	yes	188.6		140.2	yes
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	40.9		477.6		ND	yes	TR	yes	162.1		118.9	yes
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	52.6		528.4		ND	yes	TR	yes	184.2		147.3	yes
KN-04-01, without co-administration of L-arginine															
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	20.5		692.5		ND	yes	ND		231.3		357.5	yes
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	29.3		562.2		ND	yes	ND		201.3		287.8	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	26.7		625.4		ND	yes	ND		166.2		266.7	
KN-05-01, with co-administration of L-arginine															
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	56.6		348.4	yes	ND	yes	ND		155.4		154.2	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	22		428.6		ND	yes	TR	yes	188.5		132.5	yes
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	27.9		332.9	yes	ND	yes	ND		160.6		167.1	

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.2

Subject individual number, without・with co-administration of L-arginine/

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Glutamate (nmol/mL)		Glutamine (nmol/mL)		Sarcosine (nmol/mL)		α-aminoadipic acid (nmol/mL)		Proline (nmol/mL		Glycine (nmol/mL)	
				mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal
KN-07-01, with co-administration of L-arginine															
0 wks	2013/10/31 11:55	-	2013/10/31 10:35	43.2		438.1		ND	yes	ND		164.6		127	yes
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	38.5		349.2	yes	ND	yes	ND		160		101.3	yes
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	22.5		476.5		ND	yes	ND		152.6		152.7	
KN-08-01, with co-administration of L-arginine															
0 wks	-	-	2013/10/28 11:50	27.2		547.8		ND	yes	ND		149.7		180	
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	36		531.2		ND	yes	ND		159.9		186.4	
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	33.5		565.9		ND	yes	ND		153.3		174	
KN-10-01, with co-administration of L-arginine															
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	42.6		467.4		TR		TR	yes	167.6		178.3	
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	78.4	yes	394.4	yes	TR		TR	yes	144.3		130.4	yes
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	134.4	yes	306.4	yes	TR		TR	yes	122.5		73.6	yes

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.2

Subject individual number, without・with co-administration of L-arginine/

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Glutamate (nmol/mL)		Glutamine (nmol/mL)		Sarcosine (nmol/mL)		α-aminoadipic acid (nmol/mL)		Proline (nmol/mL)		Glycine (nmol/mL)	
				mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal
KN-11-01, with co-administration of L-arginine															
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	44.2		419.5	yes	TR		TR	yes	345.4	yes	197.9	
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	61		380.2	yes	TR		TR	yes	310.8	yes	158.1	
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	57.6		363	yes	TR		TR	yes	454.8	yes	171	
KN-12-01, with co-administration of L-arginine															
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	10.3	yes	425.9		ND	yes	ND		116.9		124.3	yes
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	30		461		ND	yes	ND		171.2		174.9	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	13.2		408.8	yes	ND	yes	ND		94.8		115.4	yes
KN-13-01, with co-administration of L-arginine															
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	58.1		438.8		ND	yes	TR	yes	126		135.9	yes
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	68.9	yes	412.7	yes	ND	yes	ND		132.3		132.3	yes
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:05	89.5	yes	385.2	yes	ND	yes	TR	yes	175.4		103.8	yes

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.3

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Alanine (nmol/mL) mesure-ment	Alanine (nmol/mL) ab-normal	Citrulline (nmol/mL) mesure-ment	Citrulline (nmol/mL) ab-normal	α-aminobutyric acid (nmol/mL) mesure-ment	α-aminobutyric acid (nmol/mL) ab-normal	Valine (nmol/mL) mesure-ment	Valine (nmol/mL) ab-normal	Cystine (nmol/mL) mesure-ment	Cystine (nmol/mL) ab-normal	Cystathionine (nmol/mL) mesure-ment	Cystathionine (nmol/mL) ab-normal
KN-01-01, with co-administration of L-arginine															
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	376.3		13.7	yes	7.7	yes	148.8		7.6	yes	ND	yes
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	381.6		28.3		7.2	yes	147.4	yes	8.1	yes	ND	yes
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	489.1		26		12.5		148.3		12.2	yes	ND	yes
KN-03-01, with co-administration of L-arginine															
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	429.1		17.1		13.3		272.5		14.3		ND	yes
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	484.9		23.4		24.8		337.8	yes	16.3		ND	yes
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	478.3		14.1	yes	26.3		256.5		9.4	yes	ND	yes
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	526.8	yes	15.7	yes	13.9		225.6		10.6	yes	ND	yes
KN-04-01, without co-administration of L-arginine															
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	715.4	yes	19.9		17.7		154.6		12.6	yes	ND	yes
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	617.3	yes	21.3		12		159.5		9.8	yes	ND	yes
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	537.8	yes	20.9		17.5		171.4		20		ND	yes
KN-05-01, with co-administration of L-arginine															
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	501.4		19.7		15.1		262.6		10.6	yes	ND	yes
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	570.4	yes	30.9		18.8		231.8		12.4	yes	ND	yes
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	757.4	yes	16.6	yes	27.5	yes	209		10.5	yes	ND	yes

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.3

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Alanine (nmol/mL) mesure-ment	Alanine (nmol/mL) ab-normal	Citrulline (nmol/mL) mesure-ment	Citrulline (nmol/mL) ab-normal	α-aminobutyric acid (nmol/mL) mesure-ment	α-aminobutyric acid (nmol/mL) ab-normal	Valine (nmol/mL) mesure-ment	Valine (nmol/mL) ab-normal	Cystine (nmol/mL) mesure-ment	Cystine (nmol/mL) ab-normal	Cystathionine (nmol/mL) mesure-ment	Cystathionine (nmol/mL) ab-normal
KN-07-01, with co-administration of L-arginine															
0 wks	2013/10/31 11:55	-	2013/10/31 10:35	338		26.6		8.6		195.7		11.2	yes	ND	yes
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	322.6		35.8		8.7		151.7		11.3	yes	ND	yes
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	430.1		29.7		17.9		172.8		21		ND	yes
KN-08-01, with co-administration of L-arginine															
0 wks	-	-	2013/10/28 11:50	467.2		19.1		18.3		174.4		13.1	yes	ND	yes
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	455.8		23.9		16.8		181.9		10.5	yes	ND	yes
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	453.3		33.2		15.2		201.6		17.3		ND	yes
KN-10-01, with co-administration of L-arginine															
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	609.7	yes	17.2		27	yes	250		11.3	yes	ND	yes
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	537.4	yes	12.6	yes	20.5		237.4		7.8	yes	ND	yes
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	319.7		12.4	yes	16.9		217.3		8.7	yes	ND	yes

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.3

Subject individual number, without・with co-administration of L-arginine/

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Alanine (nmol/mL)		Citrulline (nmol/mL)		α-aminobutyric acid (nmol/mL)		Valine (nmol/mL)		Cystine (nmol/mL)		Cystathionine (nmol/mL)	
				mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal
KN-11-01, with co-administration of L-arginine															
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	611.7	yes	10.9	yes	23.6		273.7		9.5	yes	ND	yes
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	611.6	yes	13.5	yes	21.2		245.6		13.6	yes	ND	yes
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	768.9	yes	12.1	yes	24.8		230		13.1	yes	ND	yes
KN-12-01, with co-administration of L-arginine															
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	508.7		14.1	yes	19.5		173.7		4.8	yes	ND	yes
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	691.2	yes	24		18.4		189.8		6	yes	ND	yes
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	440.7		16.3	yes	29.9	yes	180.3		10.2	yes	ND	yes
KN-13-01, with co-administration of L-arginine															
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	428.7		14.6	yes	5.6	yes	272.9		10.9	yes	ND	yes
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	327.9		16.4	yes	7.1	yes	226.9		7.5	yes	ND	yes
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:05	443.9		13.5	yes	13		225.5		9.8	yes	ND	yes

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.4

Subject individual number, without・with co-administration of L-arginine/

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Methionine (nmol/mL)		Isoleucine (nmol/mL)		Leucine (nmol/mL)		Tyrosine (nmol/mL)		Phenylalanine (nmol/mL)		γ-amino β-hydroxy-butyric acid (nmol/mL)	
				mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal
KN-01-01, with co-administration of L-arginine															
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	13.8	yes	53.3		98.4		37.9	yes	52.5		ND	
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	11.2	yes	40.2	yes	75.2	yes	32.2	yes	40.2	yes	ND	
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	15.5	yes	44		93.5		38.8	yes	48		ND	
KN-03-01, with co-administration of L-arginine															
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	13.6	yes	93.8		142.5		40.9		43.9		ND	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	19.7		119.9	yes	194.2	yes	57.3		53.2		ND	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	16.3	yes	78.2		133.8		43.3		46.5		ND	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	12.4	yes	77.6		127.2		41.8		45.4		ND	
KN-04-01, without co-administration of L-arginine															
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	31.1		63.1		113.6		52.8		54.2		ND	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	24.5		57.5		100.6		43		43.2		ND	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	32.8		68.8		109.3		38	yes	50.1		ND	
KN-05-01, with co-administration of L-arginine															
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	20.8		83.1		140.5		39.8	yes	62.1		ND	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	16.4	yes	71		124.8		37.9	yes	55.3		ND	
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	30.8		68.6		149.8		52.3		64.7		ND	

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.4

Subject individual number, without・with co-administration of L-arginine/

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Methionine (nmol/mL) mesure-ment	Methionine (nmol/mL) ab-normal	Isoleucine (nmol/mL) mesure-ment	Isoleucine (nmol/mL) ab-normal	Leucine (nmol/mL mesure-ment	Leucine (nmol/mL ab-normal	Tyrosine (nmol/mL) mesure-ment	Tyrosine (nmol/mL) ab-normal	Phenylalanine (nmol/mL) mesure-ment	Phenylalanine (nmol/mL) ab-normal	γ-amino β-hydroxy-butyric acid (nmol/mL) mesure-ment	γ-amino β-hydroxy-butyric acid (nmol/mL) ab-normal
KN-07-01, with co-administration of L-arginine															
0 wks	2013/10/31 11:55	-	2013/10/31 10:35	15.1	yes	67.3		111.9		53.2		58.1		ND	
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	11.5	yes	44.7		88.1		43.2		44.7		ND	
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	17.3	yes	47.6		105.9		49.4		48.5		ND	
KN-08-01, with co-administration of L-arginine															
0 wks	-	-	2013/10/28 11:50	16	yes	54.2		96.2		34	yes	41.6	yes	ND	
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	12.6	yes	50.8		95.4		29.2	yes	41.7	yes	ND	
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	16.3	yes	59.3		110.8		40.8		50.3		ND	
KN-10-01, with co-administration of L-arginine															
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	19		80.9		143.7		70.7		52.7		ND	
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	12.6	yes	68.6		120.6		67		47.7		ND	
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	10.2	yes	60.9		122.9		52.9		61.4		ND	

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.4

Subject individual number, without・with co-administration of L-arginine/

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Methionine (nmol/mL)		Isoleucine (nmol/mL)		Leucine (nmol/mL)		Tyrosine (nmol/mL)		Phenylalanine (nmol/mL)		γ-amino β-hydroxy-butyric acid (nmol/mL)	
				mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal
KN-11-01, with co-administration of L-arginine															
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	19.8		95.8		150.5		56.3		41.6	yes	ND	
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	15.8	yes	82.3		133.4		56.7		36.8	yes	ND	
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	15	yes	88.8		121		52.7		37	yes	ND	
KN-12-01, with co-administration of L-arginine															
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	13.5	yes	48.3		109.1		27.8	yes	34.8	yes	ND	
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	19.9		63.1		119.2		42.7		36.2	yes	ND	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	17.1	yes	45.5		89		32	yes	37.6	yes	ND	
KN-13-01, with co-administration of L-arginine															
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	21.7		98.7		163.8		64.9		59.5		ND	
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	11.3	yes	76.7		122.1		42.5		40.4	yes	ND	
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:05	11.4	yes	72		109.4		36.1	yes	33.7	yes	ND	

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.5

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	β-Alanine (nmol/mL)		β-amino-isobutyric acid (nmol/mL)		γ-aminobutyric acid (nmol/mL)		Mono-ethanolamine (nmol/mL)		Homocysteine (nmol/mL)		Histidine (nmol/mL)	
				mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal
KN-01-01, with co-administration of L-arginine															
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	TR		ND	yes	ND		TR		ND		75.2	
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	4	yes	ND	yes	ND		TR		ND		65.5	
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	TR		ND	yes	ND		5.5		ND		77.3	
KN-03-01, with co-administration of L-arginine															
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	5	yes	ND	yes	ND		5.3		ND		64.8	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	6.8	yes	ND	yes	ND		7.1		ND		86.2	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	5.2	yes	ND	yes	ND		8.7		ND		67.1	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	TR		ND	yes	ND		7.8		ND		68.5	
KN-04-01, without co-administration of L-arginine															
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	4.6	yes	ND	yes	ND		5.3		ND		72	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	4.9	yes	ND	yes	ND		5.6		ND		75	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	4.1	yes	ND	yes	ND		TR		ND		75	
KN-05-01, with co-administration of L-arginine															
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	11	yes	TR		ND		TR		ND		79.9	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	4.7	yes	3.4	yes	ND		8		ND		70.2	
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	TR		3.3	yes	ND		6.6		ND		82.6	

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.5

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	β-Alanine (nmol/mL)		β-amino-isobutyric acid (nmol/mL)		γ-aminobutyric acid (nmol/mL)		Mono-ethanolamine (nmol/mL)		Homocysteine (nmol/mL)		Histidine (nmol/mL)	
				mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal
KN-07-01, with co-administration of L-arginine															
0 wks	2013/10/31 11:55	-	2013/10/31 10:35	4.5	yes	ND	yes	ND		TR		ND		57	yes
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	3.7	yes	ND	yes	ND		5.4		ND		52.8	yes
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	6.5	yes	ND	yes	ND		TR		ND		74.9	
KN-08-01, with co-administration of L-arginine															
0 wks	-	-	2013/10/28 11:50	5.2	yes	ND	yes	ND		6.8		ND		59.3	
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	6.8	yes	ND	yes	ND		6.1		ND		61.7	
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	5.2	yes	ND	yes	ND		6.5		ND		63.8	
KN-10-01, with co-administration of L-arginine															
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	4.9	yes	ND	yes	ND		7		ND		80.9	
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	4.6	yes	ND	yes	ND		6.1		ND		59.7	
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	3.1	yes	ND	yes	ND		TR		ND		47.8	yes

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.5

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	β-Alanine (nmol/mL)		β-amino-isobutyric acid (nmol/m)		γ-aminobutyric acid (nmol/mL)		Mono-ethanolamine (nmol/mL)		Homocysteine (nmol/mL)		Histidine (nmol/mL)	
				mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal	mesure-ment	ab-normal
KN-11-01, with co-administration of L-arginine															
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	10.1	yes	TR		ND		6		ND		74.6	
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	4	yes	3.3	yes	ND		8.8		ND		63	
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	TR		5.5	yes	ND		7.4		ND		67.1	
KN-12-01, with co-administration of L-arginine															
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	TR		ND	yes	ND		5.1		ND		56.3	yes
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	3.3	yes	ND	yes	ND		5.6		ND		56	yes
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	TR		ND	yes	ND		8		ND		58.7	yes
KN-13-01, with co-administration of L-arginine															
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	3.9	yes	ND	yes	ND		6.3		ND		69.2	
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	4.6	yes	TR		ND		5.4		ND		57.4	yes
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:05	TR		3.1	yes	ND		5.1		ND		52.1	yes

Program Name: L080102_02.sas / Output: l080102_02.rtf
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Data Source: adsbdaa

Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.6

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	3-methyl-histidine (nmol/mL) mesure-ment	3-methyl-histidine (nmol/mL) ab-normal	1-methyl-histidine (nmol/mL) mesure-ment	1-methyl-histidine (nmol/mL) ab-normal	Carnosine (nmol/mL) mesure-ment	Carnosine (nmol/mL) ab-normal	Anserine (nmol/mL) mesure-ment	Anserine (nmol/mL) ab-normal	Tryptophan (nmol/mL) mesure-ment	Tryptophan (nmol/mL) ab-normal	Hydroxylysine (nmol/mL) mesure-ment	Hydroxylysine (nmol/mL) ab-normal
KN-01-01, with co-administration of L-arginine															
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	ND		ND		ND		ND		48.5		ND	
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	ND		6.3		ND		ND		34.7	yes	ND	
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	TR		TR		ND		ND		38.3		ND	
KN-03-01, with co-administration of L-arginine															
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	TR		ND		ND		ND		42.6		ND	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	TR		ND		ND		ND		45.9		ND	
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	TR		4.5		ND		ND		34.9	yes	ND	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	TR		ND		ND		ND		39.9		ND	
KN-04-01, without co-administration of L-arginine															
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	TR		ND		ND		ND		51.9		ND	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	TR		TR		ND		ND		40.3		ND	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	TR		12.5		ND		ND		47.3		ND	
KN-05-01, with co-administration of L-arginine															
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	TR		18.7	yes	ND		ND		53.5		ND	
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	TR		ND		ND		ND		48.1		ND	
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	TR		ND		ND		ND		57.7		ND	

Program Name: L080102_02.sas / Output: l080102_02.rtf
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Data Source: adsbdaa

Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.6

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	3-methyl-histidine (nmol/mL) mesure-ment	3-methyl-histidine (nmol/mL) ab-normal	1-methyl-histidine (nmol/mL) mesure-ment	1-methyl-histidine (nmol/mL) ab-normal	Carnosine (nmol/mL) mesure-ment	Carnosine (nmol/mL) ab-normal	Anserine (nmol/mL) mesure-ment	Anserine (nmol/mL) ab-normal	Tryptophan (nmol/mL) mesure-ment	Tryptophan (nmol/mL) ab-normal	Hydroxylysine (nmol/mL) mesure-ment	Hydroxylysine (nmol/mL) ab-normal
KN-07-01, with co-administration of L-arginine															
0 wks	2013/10/31 11:55	-	2013/10/31 10:35	TR		ND		ND		ND		38.8		ND	
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	TR		ND		ND		ND		38.8		ND	
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	4.4		8.6		ND		ND		36.9	yes	ND	
KN-08-01, with co-administration of L-arginine															
0 wks	-	-	2013/10/28 11:50	TR		ND		ND		ND		34.3	yes	ND	
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	ND		4.8		ND		ND		33.2	yes	ND	
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	TR		TR		ND		ND		39.2		ND	
KN-10-01, with co-administration of L-arginine															
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	4.6		TR		ND		ND		56.5		ND	
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	TR		TR		ND		ND		51.6		ND	
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	TR		ND		ND		ND		47		ND	

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Data Source: adsbdaa

Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.6

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	3-methyl-histidine (nmol/mL) mesure-ment	3-methyl-histidine (nmol/mL) ab-normal	1-methyl-histidine (nmol/mL) mesure-ment	1-methyl-histidine (nmol/mL) ab-normal	Carnosine (nmol/mL) mesure-ment	Carnosine (nmol/mL) ab-normal	Anserine (nmol/mL) mesure-ment	Anserine (nmol/mL) ab-normal	Tryptophan (nmol/mL) mesure-ment	Tryptophan (nmol/mL) ab-normal	Hydroxylysine (nmol/mL) mesure-ment	Hydroxylysine (nmol/mL) ab-normal
KN-11-01, with co-administration of L-arginine															
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	TR		10.4		ND		ND		41.6		ND	
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	TR		ND		ND		ND		39		ND	
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	TR		ND		ND		ND		36.6	yes	ND	
KN-12-01, with co-administration of L-arginine															
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	ND		ND		ND		ND		28.4	yes	ND	
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	ND		ND		ND		ND		24	yes	ND	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	ND		TR		ND		ND		28.6	yes	ND	
KN-13-01, with co-administration of L-arginine															
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	TR		TR		ND		ND		75	yes	ND	
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	TR		ND		ND		ND		45.3		ND	
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:05	TR		ND		ND		ND		42.4		ND	

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Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.7

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Ornithine (nmol/mL) mesurement	Ornithine (nmol/mL) abnormal	Lysine (nmol/mL) mesurement	Lysine (nmol/mL) abnormal	Arginine (nmol/mL) mesurement	Arginine (nmol/mL) abnormal
KN-01-01, with co-administration of L-arginine									
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	25.3	yes	107.8	yes	48	yes
4 wks	2013/10/31 07:00	2013/10/31 07:35	2013/10/31 09:30	108.1	yes	109.2		262.6	yes
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	161.2	yes	128.4		369.8	yes
KN-03-01, with co-administration of L-arginine									
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	96.3		100	yes	108.1	
4 wks	2014/02/03 08:30	2014/02/03 08:55	2014/02/03 11:15	164.5	yes	164		175.1	yes
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	111.9	yes	137.9		112.5	
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	153.1	yes	104.7	yes	210.2	yes
KN-04-01, without co-administration of L-arginine									
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	49.8		184.3		86.1	
4 wks	2013/12/12 11:20	2013/12/12 11:35	2013/12/12 13:00	50.4		176.8		69.8	
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	47.9		173.3		80.4	
KN-05-01, with co-administration of L-arginine									
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	109.8	yes	135.8		260.8	yes
4 wks	2013/11/29 08:00	2013/11/29 08:15	2013/11/29 11:33	128.1	yes	131.7		265.8	yes
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	69.8		149.9		148.8	yes

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Data Source: adsbdaa

Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.7

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Ornithine (nmol/mL) mesurement	Ornithine (nmol/mL) abnormal	Lysine (nmol/mL) mesurement	Lysine (nmol/mL) abnormal	Arginine (nmol/mL) mesurement	Arginine (nmol/mL) abnormal
KN-07-01, with co-administration of L-arginine									
0 wks	2013/10/31 11:55	-	2013/10/31 10:35	109.8	yes	92.4	yes	153.5	yes
4 wks	2013/11/29 07:00	2013/11/29 07:00	2013/11/29 10:54	83.1		94.9	yes	102.1	
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	64.1		142.2		99.5	
KN-08-01, with co-administration of L-arginine									
0 wks	-	-	2013/10/28 11:50	195	yes	159.1		244.7	yes
4 wks	2013/11/27 07:40	2013/11/27 08:40	2013/11/27 11:30	228.3	yes	179.5		260.7	yes
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	174.5	yes	163.6		242.4	yes
KN-10-01, with co-administration of L-arginine									
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	122.3	yes	187.4		199.8	yes
4 wks	2013/12/06 07:23	2013/12/06 07:50	2013/12/06 10:30	93.8		138.3		142.5	yes
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	133.5	yes	89.6	yes	107.3	

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Data Source: adsbdaa

Table 4.3.4-5 Specialized Tests：List of blood amino acid analyses (39 types) for blood test　No.7

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Ornithine (nmol/mL) mesurement	Ornithine (nmol/mL) abnormal	Lysine (nmol/mL) mesurement	Lysine (nmol/mL) abnormal	Arginine (nmol/mL) mesurement	Arginine (nmol/mL) abnormal
KN-11-01, with co-administration of L-arginine									
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	52.1		116		90.9	
4 wks	2014/01/10 08:00	2014/01/10 08:30	2014/01/10 10:29	66.5		134		169.5	yes
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	68.4		115.8		144.1	yes
KN-12-01, with co-administration of L-arginine									
0 wks	2013/11/17 18:00	-	2013/11/18 12:30	28.6	yes	96.1	yes	47.2	yes
4 wks	2013/12/08 18:00	2013/12/09 09:00	2013/12/09 12:10	54.8		130.2		65.1	
52 wks (or when canceled)	2014/11/16 18:00	2014/11/17 10:00	2014/11/17 12:45	34.1		124.1		56.2	
KN-13-01, with co-administration of L-arginine									
0 wks	2013/12/27 08:00	-	2013/12/27 10:18	134.1	yes	138		86.7	
4 wks	2014/01/24 11:30	2014/01/24 11:30	2014/01/24 13:10	227.5	yes	120.2		224.6	yes
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:05	284.9	yes	116.2		185.9	yes

Program Name: L080102_02.sas / Output: l080102_02.rtf
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Data Source: adsbdaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.1

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Taurine (nmol/mL)	Aspartate (nmol/mL)	Hydroxyproline (nmol/mL)	Threonine (nmol/mL)	Serine (nmol/mL)	Asparagine (nmol/mL)
Subject individual number, without・with co-administration of L-arginine/									
KN-01-01, with co-administration of L-arginine									
0 wks	2013/10/03 07:00	-	2013/10/03 14:00	15.8	ND	ND	16	17.6	7.1
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 11:19	46.1	ND	ND	22.9	15.6	6.7
KN-03-01, with co-administration of L-arginine									
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:00	50.7	ND	ND	29	29.9	7.3
KN-04-01, without co-administration of L-arginine									
0 wks	2013/11/14 12:30	-	2013/11/14 15:50	9.1	ND	ND	29.7	26.7	8
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 10:00	30.5	ND	ND	20.7	22.7	6
KN-05-01, with co-administration of L-arginine									
0 wks	2013/10/31 12:10	-	2013/10/31 14:00	9.8	ND	ND	22.7	25	7.7
52 wks (or when canceled)	-	-	2014/10/29 19:30	34.2	ND	ND	12	20.2	TR

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.1

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Taurine (nmol/mL)	Aspartate (nmol/mL)	Hydroxyproline (nmol/mL)	Threonine (nmol/mL)	Serine (nmol/mL)	Asparagine (nmol/mL)
KN-07-01, with co-administration of L-arginine									
0 wks	2013/10/31 11:55	-	2013/10/31 13:20	9.7	ND	ND	16.7	19.3	5.1
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:40	66.3	ND	ND	17.2	16.1	5.6
KN-08-01, with co-administration of L-arginine									
0 wks	-	-	2013/10/28 10:40	12.4	ND	ND	28	28.2	9.6
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 10:25	39.6	ND	ND	21.8	21.3	8.2
KN-10-01, with co-administration of L-arginine									
0 wks	2013/11/06 07:28	-	2013/11/06 11:30	14	ND	ND	25.4	32.9	6
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 12:30	51.6	ND	ND	14.2	21.9	TR
KN-13-01, with co-administration of L-arginine									
0 wks	2013/12/27 08:00	-	2013/12/27 11:00	7.9	ND	ND	17.5	20.6	7.3
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 13:40	26.5	ND	ND	14.5	12.9	5.3

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.2

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Glutamate (nmol/mL)	Glutamine (nmol/mL)	Sarcosine (nmol/mL)	α-aminoadipic acid (nmol/mL)	Proline (nmol/mL)	Glycine (nmol/mL)
KN-01-01, with co-administration of L-arginine									
0 wks	2013/10/03 07:00	-	2013/10/03 14:00	ND	421.4	ND	ND	ND	5.6
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 11:19	ND	496.3	ND	ND	ND	4.9
KN-03-01, with co-administration of L-arginine									
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:00	ND	613.4	ND	ND	ND	8.9
KN-04-01, without co-administration of L-arginine									
0 wks	2013/11/14 12:30	-	2013/11/14 15:50	ND	529.9	ND	ND	ND	5.9
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 10:00	ND	495.8	ND	ND	ND	4.9
KN-05-01, with co-administration of L-arginine									
0 wks	2013/10/31 12:10	-	2013/10/31 14:00	ND	506.3	ND	ND	ND	4.6
52 wks (or when canceled)	-	-	2014/10/29 19:30	ND	434.1	ND	ND	ND	3.1

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.2

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Glutamate (nmol/mL)	Glutamine (nmol/mL)	Sarcosine (nmol/mL)	α-aminoadipic acid (nmol/mL)	Proline (nmol/mL)	Glycine (nmol/mL)
KN-07-01, with co-administration of L-arginine									
0 wks	2013/10/31 11:55	-	2013/10/31 13:20	ND	478.2	ND	ND	ND	4.1
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:40	ND	455.1	ND	ND	ND	4.3
KN-08-01, with co-administration of L-arginine									
0 wks	-	-	2013/10/28 10:40	ND	621.4	ND	ND	ND	6.5
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 10:25	ND	589.1	ND	ND	ND	6
KN-10-01, with co-administration of L-arginine									
0 wks	2013/11/06 07:28	-	2013/11/06 11:30	ND	476.9	ND	ND	ND	5.2
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 12:30	ND	462.4	ND	ND	ND	5.5
KN-13-01, with co-administration of L-arginine									
0 wks	2013/12/27 08:00	-	2013/12/27 11:00	ND	453.3	ND	ND	ND	6.9
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 13:40	ND	445	ND	ND	ND	4.6

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.3

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Alanine (nmol/mL)	Citrulline (nmol/mL)	α-aminobutyric acid (nmol/mL)	Valine (nmol/mL)	Cystine (nmol/mL)	Cystathionine (nmol/mL)
Subject individual number, without・with co-administration of L-arginine/									
KN-01-01, with co-administration of L-arginine									
0 wks	2013/10/03 07:00	-	2013/10/03 14:00	63.4	ND	TR	14.3	ND	ND
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 11:19	56.9	TR	TR	14	ND	ND
KN-03-01, with co-administration of L-arginine									
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:00	76.2	ND	7.9	35.2	ND	ND
KN-04-01, without co-administration of L-arginine									
0 wks	2013/11/14 12:30	-	2013/11/14 15:50	58.8	TR	TR	10.8	ND	ND
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 10:00	34.9	TR	ND	12	ND	ND
KN-05-01, with co-administration of L-arginine									
0 wks	2013/10/31 12:10	-	2013/10/31 14:00	100.1	TR	TR	25	ND	ND
52 wks (or when canceled)	-	-	2014/10/29 19:30	69	ND	TR	17.8	ND	ND

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.3

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Alanine (nmol/mL	Citrulline (nmol/mL)	α-aminobutyric acid (nmol/mL)	Valine (nmol/mL)	Cystine (nmol/mL)	Cystathionine (nmol/mL)
Subject individual number, without・with co-administration of L-arginine/									
KN-07-01, with co-administration of L-arginine									
0 wks	2013/10/31 11:55	-	2013/10/31 13:20	57.7	ND	TR	17.1	ND	ND
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:40	45.6	TR	TR	18.5	ND	ND
KN-08-01, with co-administration of L-arginine									
0 wks	-	-	2013/10/28 10:40	74.1	TR	5.3	23.6	ND	ND
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 10:25	61.5	TR	TR	19.2	ND	ND
KN-10-01, with co-administration of L-arginine									
0 wks	2013/11/06 07:28	-	2013/11/06 11:30	87.3	ND	5.7	22.5	ND	ND
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 12:30	48.2	ND	5.2	20.4	ND	ND
KN-13-01, with co-administration of L-arginine									
0 wks	2013/12/27 08:00	-	2013/12/27 11:00	77.7	ND	ND	23.3	ND	ND
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 13:40	63.9	ND	TR	21.3	ND	ND

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.4

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Methionine (nmol/mL)	Isoleucine (nmol/mL)	Leucine (nmol/mL)	Tyrosine (nmol/mL)	Phenylalanine (nmol/mL)	γ-amino β-hydroxy-butyric acid (nmol/mL)
KN-01-01, with co-administration of L-arginine									
0 wks	2013/10/03 07:00	-	2013/10/03 14:00	2.7	5.5	14.9	7.6	10.3	ND
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 11:19	2.9	5	14	6.8	7.4	ND
KN-03-01, with co-administration of L-arginine									
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:00	4.2	11.8	25.9	9	10.1	ND
KN-04-01, without co-administration of L-arginine									
0 wks	2013/11/14 12:30	-	2013/11/14 15:50	3.8	5.1	12.1	7.4	9.1	ND
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 10:00	3.5	5.1	10.7	5.1	7.7	ND
KN-05-01, with co-administration of L-arginine									
0 wks	2013/10/31 12:10	-	2013/10/31 14:00	3.5	7.8	21.5	6.1	10.6	ND
52 wks (or when canceled)	-	-	2014/10/29 19:30	TR	5.4	15.7	4.3	8.7	ND

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.4

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Methionine (nmol/mL)	Isoleucine (nmol/mL)	Leucine (nmol/mL)	Tyrosine (nmol/mL)	Phenylalanine (nmol/mL)	γ-amino β-hydroxy-butyric acid (nmol/mL)
KN-07-01, with co-administration of L-arginine									
0 wks	2013/10/31 11:55	-	2013/10/31 13:20	2.3	5.7	15.6	9.4	9.1	ND
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:40	2.7	5.6	15.8	8.8	8.8	ND
KN-08-01, with co-administration of L-arginine									
0 wks	-	-	2013/10/28 10:40	3.7	9.3	21.6	6.6	10.8	ND
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 10:25	3.2	7.1	17.6	7.2	9.7	ND
KN-10-01, with co-administration of L-arginine									
0 wks	2013/11/06 07:28	-	2013/11/06 11:30	2.7	8	19.9	10	8.4	ND
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 12:30	2.2	7	19.1	9.3	11.9	ND
KN-13-01, with co-administration of L-arginine									
0 wks	2013/12/27 08:00	-	2013/12/27 11:00	2.6	7.7	20.1	9	10	ND
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 13:40	2.2	7.9	18.4	6.8	7.4	ND

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.5

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	β-Alanine (nmol/mL)	β-amino-isobutyric acid (nmol/mL)	γ-aminobutyric acid (nmol/mL)	Mono-ethanolamine (nmol/mL)	Homocysteine (nmol/mL)	Histidine (nmol/mL)
Subject individual number, without・with co-administration of L-arginine/									
KN-01-01, with co-administration of L-arginine									
0 wks	2013/10/03 07:00	-	2013/10/03 14:00	ND	ND	ND	8.7	ND	15.6
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 11:19	ND	ND	ND	8.2	ND	12.2
KN-03-01, with co-administration of L-arginine									
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:00	ND	ND	ND	10.7	ND	14.8
KN-04-01, without co-administration of L-arginine									
0 wks	2013/11/14 12:30	-	2013/11/14 15:50	TR	ND	ND	9.2	ND	14.7
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 10:00	ND	ND	ND	8.5	ND	13.8
KN-05-01, with co-administration of L-arginine									
0 wks	2013/10/31 12:10	-	2013/10/31 14:00	TR	ND	ND	11	ND	16.2
52 wks (or when canceled)	-	-	2014/10/29 19:30	ND	ND	ND	9.7	ND	13.6

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.5

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	β-Alanine (nmol/mL)	β-amino-isobutyric acid (nmol/mL)	γ-aminobutyric acid (nmol/mL)	Mono-ethanolamine (nmol/mL)	Homocysteine (nmol/mL)	Histidine (nmol/mL)
Subject individual number, without・with co-administration of L-arginine/									
KN-07-01, with co-administration of L-arginine									
0 wks	2013/10/31 11:55	-	2013/10/31 13:20	TR	ND	ND	8.9	ND	11.2
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:40	ND	ND	ND	8.1	ND	12.2
KN-08-01, with co-administration of L-arginine									
0 wks	-	-	2013/10/28 10:40	3	ND	ND	8.3	ND	12.7
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 10:25	ND	ND	ND	6.9	ND	10.8
KN-10-01, with co-administration of L-arginine									
0 wks	2013/11/06 07:28	-	2013/11/06 11:30	TR	ND	ND	11.5	ND	15
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 12:30	ND	ND	ND	8.7	ND	12.1
KN-13-01, with co-administration of L-arginine									
0 wks	2013/12/27 08:00	-	2013/12/27 11:00	ND	ND	ND	11.1	ND	12.4
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 13:40	ND	ND	ND	10.2	ND	9.2

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.6

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	3-methyl-histidine (nmol/mL)	1-methyl-histidine (nmol/mL)	Carnosine (nmol/mL)	Anserine (nmol/mL)	Tryptophan (nmol/mL)	Hydroxylysine (nmol/mL)
Subject individual number, without・with co-administration of L-arginine/									
KN-01-01, with co-administration of L-arginine									
0 wks	2013/10/03 07:00	-	2013/10/03 14:00	ND	ND	ND	ND	ND	ND
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 11:19	ND	ND	ND	ND	ND	ND
KN-03-01, with co-administration of L-arginine									
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:00	ND	ND	ND	ND	ND	ND
KN-04-01, without co-administration of L-arginine									
0 wks	2013/11/14 12:30	-	2013/11/14 15:50	ND	ND	ND	ND	ND	ND
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 10:00	ND	ND	ND	ND	ND	ND
KN-05-01, with co-administration of L-arginine									
0 wks	2013/10/31 12:10	-	2013/10/31 14:00	ND	ND	ND	ND	ND	ND
52 wks (or when canceled)	-	-	2014/10/29 19:30	ND	ND	ND	ND	ND	ND

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.6

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	3-methyl-histidine (nmol/mL)	1-methyl-histidine (nmol/mL)	Carnosine (nmol/mL)	Anserine (nmol/mL)	Tryptophan (nmol/mL)	Hydroxylysine (nmol/mL)
KN-07-01, with co-administration of L-arginine									
0 wks	2013/10/31 11:55	-	2013/10/31 13:20	ND	ND	ND	ND	ND	ND
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:40	ND	ND	ND	ND	TR	ND
KN-08-01, with co-administration of L-arginine									
0 wks	-	-	2013/10/28 10:40	ND	ND	ND	ND	ND	ND
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 10:25	ND	ND	ND	ND	ND	ND
KN-10-01, with co-administration of L-arginine									
0 wks	2013/11/06 07:28	-	2013/11/06 11:30	ND	ND	ND	ND	ND	ND
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 12:30	ND	ND	ND	ND	ND	ND
KN-13-01, with co-administration of L-arginine									
0 wks	2013/12/27 08:00	-	2013/12/27 11:00	ND	ND	ND	ND	ND	ND
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 13:40	ND	ND	ND	ND	ND	ND

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.7

weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Ornithine (nmol/mL)	Lysine (nmol/mL)	Arginine (nmol/mL)
Subject individual number, without・with co-administration of L-arginine/						
KN-01-01, with co-administration of L-arginine						
0 wks	2013/10/03 07:00	-	2013/10/03 14:00	2.8	22.5	21.6
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 11:19	4.5	21.3	43.7
KN-03-01, with co-administration of L-arginine						
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:00	5.9	22.6	29.5
KN-04-01, without co-administration of L-arginine						
0 wks	2013/11/14 12:30	-	2013/11/14 15:50	4.1	29.5	23.9
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 10:00	3.1	25.9	20.1
KN-05-01, with co-administration of L-arginine						
0 wks	2013/10/31 12:10	-	2013/10/31 14:00	4.8	19	49.1
52 wks (or when canceled)	-	-	2014/10/29 19:30	3.4	11.9	47.8

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-6 Specialized Tests : List of CSF amino acid analyses (39 types) for CSF test No.7

Subject individual number, without・with co-administration of L-arginine/ weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Ornithine (nmol/mL)	Lysine (nmol/mL)	Arginine (nmol/mL)
KN-07-01, with co-administration of L-arginine						
0 wks	2013/10/31 11:55	-	2013/10/31 13:20	5	17.7	34.7
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:40	4.5	24.6	34.1
KN-08-01, with co-administration of L-arginine						
0 wks	-	-	2013/10/28 10:40	8.4	25.6	52.7
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 10:25	5.7	24.2	49.5
KN-10-01, with co-administration of L-arginine						
0 wks	2013/11/06 07:28	-	2013/11/06 11:30	5.1	24.1	34.3
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 12:30	5.1	20.5	21.6
KN-13-01, with co-administration of L-arginine						
0 wks	2013/12/27 08:00	-	2013/12/27 11:00	6.1	21.9	24.7
52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 13:40	9.8	18.9	26.7

Program Name: L080102_03.sas / Output: l080102_03_a.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adscsfaa

Table 4.3.4-7 Specialized Tests: Peripheral blood leukocyte examination (Safety Analysis)

Subject identification number, without・with the co-administration of L-arginine/ Weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Mitochondrial gene mutation rate of blood leukocytes (%)	$tRNA^{Leu(UUR)}$ taurine modification rate (%)	NADH dehydrogenase 6 protein mass (fold)
KN-01-01, with the co-administration of L-arginine						
0 wks	2013/10/03 07:00	-	2013/10/03 12:30	28.7	30.97	1.43
52 wks (or when canceled)	2014/10/02 07:00	2014/10/02 07:05	2014/10/02 08:40	33.8	42.28	1.37
KN-03-01, with the co-administration of L-arginine						
0 wks	2014/01/06 12:30	-	2014/01/06 16:15	39.4	29.65	1.01
unscheduled test	2014/04/18 08:00	2014/04/18 07:00	2014/04/18 14:30	39	27.02	0.94
52 wks (or when canceled)	2014/12/22 11:30	2014/12/22 12:00	2014/12/22 14:20	38.6	58.12	1.02
KN-04-01, without the co-administration of L-arginine						
0 wks	2013/11/14 12:30	-	2013/11/14 13:50	30.9	25.54	0.37
52 wks (or when canceled)	2014/11/13 07:30	2014/11/13 07:40	2014/11/13 09:10	29.2	46.43	0.53
KN-05-01, with the co-administration of L-arginine						
0 wks	2013/10/31 12:10	-	2013/10/31 13:21	53	29.95	0.42
52 wks (or when canceled)	2014/11/05 19:00	2014/11/05 19:36	2014/11/06 08:20	54.3	67.16	0.37

Program Name: L080102_03.sas / Output: l080102_03_b.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adsbl

Table 4.3.4-7 Specialized Tests: Peripheral blood leukocyte examination (Safety Analysis)

Subject identification number, without・with the co-administration of L-arginine/ Weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Mitochondrial gene mutation rate of blood leukocytes (%)	$tRNA^{Leu(UUR)}$ taurine modification rate (%)	NADH dehydrogenase 6 protein mass (fold)
KN-07-01, with the co-administration of L-arginine						
0 wks	2013/10/31 11:55	-	2013/10/31 10:35	43.4	31.5	1.08
52 wks (or when canceled)	2014/11/06 13:30	2014/11/06 06:30	2014/11/06 14:55	44	33.74	1.37
KN-08-01, with the co-administration of L-arginine						
0 wks	-	-	2013/10/28 11:50	29.5	34.25	1.87
52 wks (or when canceled)	2014/10/22 08:00	2014/10/22 08:15	2014/10/22 11:15	26.7	30.65	1.62
KN-10-01, with the co-administration of L-arginine						
0 wks	2013/11/06 07:28	-	2013/11/06 10:20	65.8	33.32	0.83
52 wks (or when canceled)	2014/11/11 08:15	2014/11/11 08:40	2014/11/11 11:50	66.2	34.5	0.86
KN-11-01, with the co-administration of L-arginine						
0 wks	2013/12/09 13:00	-	2013/12/09 14:28	57.8	38.48	
52 wks (or when canceled)	2014/12/01 08:20	2014/12/01 08:33	2014/12/01 11:15	56.9	28.35	

Program Name: L080102_03.sas / Output: l080102_03_b.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adsbl

Table 4.3.4-7 Specialized Tests: Peripheral blood leukocyte examination (Safety Analysis)

Subject identification number, without・with the co-administration of L-arginine/	Weeks	Date and time of the dietary intake just before administration of taurine	Date and time of administration of taurine	Date and time of blood collection	Mitochondrial gene mutation rate of blood leukocytes (%)	$tRNA^{Leu(UUR)}$ taurine modification rate (%)	NADH dehydrogenase 6 protein mass (fold)
KN-13-01, with the co-administration of L-arginine							
	0 wks	2013/12/27 08:00	-	2013/12/27 10:18	21.5	38.53	1.48
	52 wks (or when canceled)	2014/12/19 11:30	2014/12/19 11:50	2014/12/19 14:05	19.1	56.9	1.43

Program Name: L080102_03.sas / Output: l080102_03_b.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adsbl

Table 4.3.5-1 Change in physical examinations (Safety Analysis)

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks (or when cancelled) N = 10
Systolic BP (mmHg)						
n	10	10	10	10	10	10
Mean	119.7	112.1	115.3	107.4	112.3	112.4
SD	13.77	14.62	16.73	8.80	10.07	8.82
Median	119.5	113.0	118.0	107.5	111.0	114.0
Minimum, Maximum	100, 147	95, 133	87, 138	97, 120	95, 127	100, 124
Diastolic BP (mmHg)						
n	10	10	10	10	10	10
Mean	73.5	72.7	73.3	68.6	73.0	76.1
SD	12.94	11.47	11.59	12.90	11.13	13.76
Median	72.5	73.5	72.0	70.5	75.0	73.0
Minimum, Maximum	52, 93	55, 88	53, 91	49, 85	54, 90	55, 94
Pulse (beats/min)						
n	10	10	10	10	10	10
Mean	86.3	91.2	92.6	85.5	87.2	94.3
SD	15.68	17.75	16.57	14.84	14.97	14.02
Median	86.5	94.0	91.5	85.5	87.0	95.0
Minimum, Maximum	64, 111	57, 123	68, 120	56, 111	61, 107	74, 122

Program Name: T080103.sas / Output: t080103.rtf
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Data Source: adpe

Table 4.3.5-1 Change in physical examinations (Safety Analysis)

	0 wks N = 10	4 wks N = 10	12 wks N = 10	24 wks N = 10	36 wks N = 10	52 wks(or when cancelled) N = 10
Body weight (kg)						
n	10	10	10	10	10	10
Mean	41.94	42.56	42.72	41.62	41.89	41.99
SD	8.346	9.028	8.929	8.622	8.771	8.761
Median	41.60	41.70	41.65	39.90	41.50	42.15
Minimum, Maximum	32.0, 59.4	31.6, 62.5	32.0, 63.0	31.4, 62.3	31.4, 62.5	30.2, 61.7
Body temperature (℃)						
n	10	10	10	10	10	10
Mean	36.45	36.42	36.51	36.61	36.35	36.47
SD	0.331	0.537	0.401	0.292	0.384	0.850
Median	36.50	36.60	36.55	36.55	36.45	36.60
Minimum, Maximum	35.9, 36.9	35.3, 37.0	35.7, 37.0	36.3, 37.1	35.8, 37.1	35.1, 38.1

Program Name: T080103.sas / Output: t080103.rtf
Date of Table Generation: 2015-02-17 21:05
Data Source: adpe

Table 4.3.5-2 List of physical examinations (Safety Analysis)

Subject identification number, without・with the co-administration of L-arginine /	Blood Pressure and Pulse (sitting at rest)						Physical measurement			
weeks	Date	Systolic BP (mmHg)	Abnormal / Abnormal changes	Diastolic BP (mmHg)	Abnormal / Abnormal changes	Pulse (beats/min)	Abnormal / Abnormal changes	Date	Body temperature (°C)	Abnormal / Abnormal changes	Body weight (kg)
KN-01-01, with the co-administration of L-arginine											
-1 wks	2013/10/03	100		71		83		2013/10/03	-		33.1
0 wks	-							2013/10/03	36.7		-
4 wks	2013/10/31	116		79		98		2013/10/31	36.6		34.9
12 wks	2013/12/26	102		65		84		2013/12/26	35.7		33.9
24 wks	2014/03/20	120		79		92		2014/03/20	36.4		35.2
36 wks	2014/06/12	108		84		104		2014/06/12	36.5		35.6
52 wks (or when cancelled)	2014/10/02	104		75		94		2014/10/02	35.8		36.2
KN-03-01, with the co-administration of L-arginine											
-1 wks	-							2014/01/06	-		45.2
0 wks	2014/01/06	115		74		68		2014/01/06	35.9		-
4 wks	2014/02/03	110		62		72		2014/02/03	35.3		45.9
12 wks	2014/03/31	100		66		68		2014/03/31	36.5		47.1
unscheduled test	2014/04/18	97		53		68		2014/04/18	36.7		45
24 wks	2014/06/09	100		57		56		2014/06/09	36.3		39.6
36 wks	2014/09/01	95		62		61		2014/09/01	35.9		42.3
52 wks (or when cancelled)	2014/12/22	105		62		77		2014/12/22	36.8		45.7

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Data Source: adpe

Table 4.3.5-2 List of physical examinations (Safety Analysis)

Subject identification number, without・with the co-administration of L-arginine /

	Blood Pressure and Pulse (sitting at rest)						Physical measurement			
weeks	Date	Systolic BP (mmHg)	Abnormal / Abnormal changes	Diastolic BP (mmHg)	Abnormal / Abnormal changes	Pulse (beats/min)	Abnormal/ Abnormal changes	Date	Body temp rature (°C)	Abnormal / Abnormal changes	Body weight (kg)
KN-04-01, without the co-administration of L-arginine											
-1 wks	2013/11/07	119		67		78		2013/11/07	-		41.3
0 wks	2013/11/14	124		65		111	yes	2013/11/14	36.6		41.4
4 wks	2013/12/12	96		57		85		2013/12/12	36.3		43
12 wks	2014/02/06	119		68		87		2014/02/06	36.1		41.7
24 wks	2014/05/09	104		66		81		2014/05/09	36.9		42.1
36 wks	2014/07/18	102		67		77		2014/07/18	36.4		43.2
52 wks (or when cancelled)	2014/11/13	124		90	yes	99		2014/11/13	36.5		43.2
KN-05-01, with the co-administration of L-arginine											
-1 wks	2013/10/31	101		61		85		2013/10/31	-		46
0 wks	2013/11/01	114		67		81		2013/11/01	36.6		46
4 wks	2013/11/29	96		55		88		2013/11/29	36.4		48.4
12 wks	2014/01/24	87	yes	53		95		2014/01/24	37	yes	46.9
24 wks	2014/04/18	97		49	yes	83		2014/04/18	37.1	yes	47.1
36 wks	2014/07/04	109		54		96		2014/07/04	35.8		46
52 wks (or when cancelled)	2014/11/07	103		55		100		2014/11/07	35.8		44.8

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Table 4.3.5-2 List of physical examinations (Safety Analysis)

Subject identification number, without・with the co-administration of L-arginine /

	Blood Pressure and Pulse (sitting at rest)						Physical measurement			
weeks	Date	Systolic BP (mmHg)	Abnormal / Abnormal changes	Diastolic BP (mmHg)	Abnormal / Abnormal changes	Pulse (beats/min)	Abnormal / Abnormal changes	Date	Body temperature (°C)	Abnormal / Abnormal changes	Body weight (kg)
KN-07-01, with the co-administration of L-arginine											
-1 wks	2013/10/31	114		76		92		2013/10/31	-		41.8
0 wks	2013/10/31	114		76		92		2013/10/31	36.9		41.8
4 wks	2013/11/29	95		74		95		2013/11/29	37	yes	40.4
12 wks	2014/01/24	117		82		108		2014/01/24	36.9		41.6
24 wks	2014/04/18	100		69		88		2014/04/18	36.5		39.9
36 wks	2014/07/18	112		73		80		2014/07/18	37.1	yes	40.7
52 wks (or when cancelled)	2014/11/06	113		71		74		2014/11/06	36.9		40.5
KN-08-01, with the co-administration of L-arginine											
-1 wks	2013/10/23	115		89		70		2013/10/23	-		48.2
0 wks	2013/10/28	124		85		64		2013/10/28	36.3		48
4 wks	2013/11/27	119		83		57		2013/11/27	36.6		46.3
12 wks	2014/01/22	102		76		71		2014/01/22	36.4		46.1
unscheduled test	2014/03/19	105		69		75		2014/03/19	37	yes / yes	
unscheduled test	2014/03/24	128		75		78		2014/03/24	36.3		
24 wks	2014/04/16	114		85		75		2014/04/16	36.3		44.1
36 wks	2014/07/09	110		78		72		2014/07/09	36.1		44.3
52 wks (or when cancelled)	2014/10/22	117		89		86		2014/10/22	36.7		44.4

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Table 4.3.5-2 List of physical examinations (Safety Analysis)

Subject identification number, without・with the co-administration of L-arginine / weeks	Blood Pressure and Pulse (sitting at rest)						Physical measurement			
	Date	Systolic BP (mmHg)	Abnormal / Abnormalchanges	Diastolic BP (mmHg)	Abnormal / Abnormal changes	Pulse (beats/min)	Abnormal / Abnormal changes	Date	Body temperature (°C)	Abnormal / Abnormal changes	Body weight (kg)
KN-10-01, with the co-administration of L-arginine											
-1 wks	2013/11/05	108		68		102		2013/11/05	-		34.2
0 wks	2013/11/07	103		52		96		2013/11/07	36		33.4
4 wks	2013/12/06	101		72		93		2013/12/06	36.8		33.6
12 wks	2014/01/29	127		78		109		2014/01/29	36.8		35.5
24 wks	2014/04/23	97		50		101		2014/04/23	36.4		34.6
36 wks	2014/07/23	113		64		88		2014/07/23	36.1		32.4
52 wks (or when cancelled)	2014/11/11	100		70		122	yes / yes	2014/11/11	38.1	yes / yes	32.1
KN-11-01, with the co-administration of L-arginine											
-1 wks	2013/12/09	124		62		72		2013/12/09	-		39.1
0 wks	2013/12/09	124		62		72		2013/12/09	36.8		39.1
4 wks	2014/01/10	133		73		123	yes	2014/01/10	36.6		39
12 wks	2014/02/25	131		67		88		2014/02/25	36.6		39.4
24 wks	2014/05/26	113		72		80		2014/05/26	36.6		39.9
36 wks	2014/08/18	122		81		86		2014/08/18	36.6		40.5
52 wks (or when cancelled)	2014/12/01	120		65		89		2014/12/01	35.9		41.1

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Table 4.3.5-2 List of physical examinations (Safety Analysis)

Subject identification number, without・with the co-administration of L-arginine /

	Blood Pressure and Pulse (sitting at rest)						Physical measurement			
weeks	Date	Systolic BP (mmHg)	Abnormal / Abnormal changes	Diastolic BP (mmHg)	Abnormal / Abnormal changes	Pulse (beats/min)	Abnormal / Abnormal changes	Date	Body temperature (°C)	Abnormal / Abnormal changes	Body weight (kg)
KN-12-01, with the co-administration of L-arginine											
-1 wks	2013/11/11	145	yes	89		113	yes	2013/11/11	-		32.6
0 wks	2013/11/18	132		90	yes	90		2013/11/18	36.4		32
4 wks	2013/12/09	125		84		100		2013/12/09	36.9		31.6
12 wks	2014/02/10	130		87		120	yes	2014/02/10	36.8		32
24 wks	2014/04/28	111		79		88		2014/04/28	36.6		31.4
36 wks	2014/07/28	127		90	yes	107		2014/07/28	36.5		31.4
52 wks (or when cancelled)	2014/11/17	123		94	yes	96		2014/11/17	37.1	yes	30.2
KN-13-01, with the co-administration of L-arginine											
-1 wks	2013/12/27	147	yes	93	yes	106		2013/12/27	-		59.4
0 wks	2013/12/27	147	yes	93	yes	106		2013/12/27	36.3		59.4
4 wks	2014/01/24	130		88		101		2014/01/24	35.7		62.5
12 wks	2014/03/14	138		91	yes	96		2014/03/14	36.3		63
24 wks	2014/05/30	118		80		111	yes	2014/05/30	37	yes	62.3
36 wks	2014/08/22	125		77		101		2014/08/22	36.5		62.5
52 wks (or when cancelled)	2014/12/19	115		90	yes	106		2014/12/19	35.1		61.7

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