PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Randomized placebo-controlled multicenter trial to Evaluate the efficacy and safety of JTR-161, allogeneic human dental Pulp stem cells, in patients with Acute Ischemic stRoke (J-REPAIR)
AUTHORS	Suda, Satoshi; Nito, Chikako; Ihara, Masafumi; Iguchi, Yasuyuki; Urabe, Takao; Matsumaru, Yuji; Sakai, Nobuyuki; Kimura, Kazumi

VERSION 1 – REVIEW

REVIEWER	Ornello, Raffaele University of L'Aquila Department of Clinical Sciences and Applied Biotechnology Personal fees from Novartis, Teva, Eli Lilly. Non-financial relationships with Novartis, Allergan, Teva.
REVIEW RETURNED	10-Sep-2021

GENERAL COMMENTS	Authors presented a protocol for a trial of stem cell transplantation in patients with ischemic stroke. The topic is interesting; however, some more details should be added. 1 - The phase of the trial should be specified. Maybe this is a phase 2 trial, but I am unsure. 2 - I suggest adding more details on the rationale of the trial. Are there any prior evidence of the effectiveness of dental stem cells on stroke outcome? 3 - Why use the past to report the protocol of a study yet to be performed? 4 - How did Authors prepare placebo? Will patients' masking be granted? 5 - Will patients treated with revascularization treatments (i.v. thrombolysis, endovascular treatments) be included in the trial?

REVIEWER	de Celis-Ruiz, Elena La Paz University Hospital Biomedical Research Foundation
REVIEW RETURNED	21-Oct-2021

GENERAL COMMENTS	The authors have proposed an interesting first-in-human clinical trial protocol concerning treatment with dental-pulp tissue-derived stem cells (DPSCs) in ischemic stroke in the first 48 hours since symptom onset. However, there are some points that the authors should clarify: • Please define the clinical trial phase, as it is not mentioned on the manuscript nor in the ClinicalTrials.gov registry. It seems that it would be a phase IIA / IIB as it is a first-in-human trial and has a dose-finding design. However, in these conditions, the primary endpoint should concern also safety matters. It is remarkable that

	there is no mention in the introduction section regarding possible adverse events with these cells in ischemic stroke pre-clinical studies and safety issues regarding cell therapy with other cell types in human stroke clinical trials or with DPSCs in human trials for other conditions other than stroke (if existing). • In the study design section, authors mention that a Data and Safety Monitoring Board (DSMB) recommend advancing to the next cohort only when there are no product-related serious adverse events, including 2 or more deaths in a cohort. However, deaths due to cerebral infarction including concomitant symptoms or due to pretreatment with rt-PA and / or endovascular treatment are excluded as causes of death in this sense. Please specify what symptoms are considered by the authors as "concomitant symptoms" in ischemic stroke, in particular if pulmonary infections or other systemic infections are included in this consideration. This point must be clarified, especially as this is the first in-human trial using this cell type and authors mention the fact that this cell type exerts more potent immunosuppressive effects than BM-MSCs. • Comparing information from the study protocol manuscript and information available in Clinical Trials.gov the actual recruitment state and estimated trial initiation and study end dates do not seem clear. Please clarify if all patients have already been included and are currently in follow-up period. • On the first line of the introduction, the authors mention that "stroke is the most prevalent cerebrovascular disease worldwide, and still one of the leading causes of death and disability", however, the cited reference only refers to Japan and is outdated (published on 2013, refers to epidemiological studies performed more than 10 years ago). • Concerning inclusion/exclusion criteria: if reperfusion therapies are administered, is there a pre-defined time-point after these therapies in which screening NIHSS will be performed (considering that there could be a significant improvement in neurological function). If so, please specify in the manuscript. Also, is drug or alcohol abuse permitted? This is a usual exclusion criteria in stroke clinical trials. • Could the authors explain the reason for including penumbra region volume in exploratory analysis? This imaging parameter does not seem to be very relevant in this clinical trial, as the hypothetic mechanism of action of the DPSCs is not related to reperfusion and no further perfusion measurements are made after the pre-dosing time-point. • Concerning “Procedures”: o Apart from the DPSCs, what other components are present in the study product (excipients)? Which are the components of the placebo solution? o It would be interesting to have a basal pre-stroke BI assessment, particulary if it will be part of the primary endpoint. Can the authors explain the reason for not performing this measurement? • In the “Outcome measures” section: o Safety assessments should be included in the primary endpoint, considering the first-in-human condition of this study. o Please clarify if the difference between the secondary endpoint (5) and the primary endpoint is that it includes patients from cohorts 1 and 2 in addition to cohort 3. o Consider renaming secondary endpoint (6) "excellent outcome" (mRS <2, improvement in NIHSS >75% and BI > 95) as it may be confused easily with the study primary endpoint and secondary. • Sample size estimates: could the authors please explain the method for calculating sample size. • “Study organization and funding” section: Contact data of the

	sponsor should appear on the manuscript, on this section or on the title page. Also, the role of study sponsors and funders in the decision to submit results for publication should be specified. • "Ethics and dissemination": Protocol date and approved version should be mentioned in this section.

VERSION 1 – AUTHOR RESPONSE

Reviewer #1
Comment 1-1
The phase of the trial should be specified. Maybe this is a phase 2 trial, but I am unsure.
Response 1-1
Our study is a phase 1/2 trial. This is shown in the manuscript.
Page 3, line 45
This is a first-in-human, randomized, double-blind, placebo-controlled, multicenter, phase 1/2 clinical trial
Page 4, line 63
This study is a first-in-human, randomized, double-blind, placebo-controlled, phase 1/2 clinical trial
Page 6, line 118
The aims of this phase 1/2 study are

Comment 1-2
I suggest adding more details on the rationale of the trial. Are there any prior evidence of the effectiveness of dental stem cells on stroke outcome?
Response 1-2
We have added details in the introduction to clarify the background of cell therapy using BM-MSCs in patients with acute ischemic stroke and rationale for JTR-161 as a treatment for acute ischemic stroke.
Page 5, line 84 – 86
Administration of human BM-MSCs was safe and well tolerated in patients with acute ischemic stroke, but no significant clinical improvement was observed.7,8
Page 5, line 96 – 101
Sakai et al.14 reported that human DPSC transplantation into the completely transected spinal cord of adult rats resulted in marked recovery of hind limb locomotor functions, whereas transplantation of human BM-MSC or skin-derived fibroblasts led to substantially less recovery of locomotor function. Based on a rat stroke model and an in vitro model of ischemia15, human DPSCs are reported to be a better source of cell therapy for ischemic stroke than human BM-MSCs.
Page 6, line 105 – 111
Preclinical toxicological study of a single intravenous administration of JTR-161 to male and female nude rats showed no notable toxicological findings two weeks after administration (In house data). There were no notable findings regarding tumorigenicity 16 weeks after administration. Furthermore, no scaffold-independent proliferation ability was observed. Regarding non-cellular components of the study product and impurities derived from the manufacturing process, because the amount of residual impurities was low, there were negligible concerns regarding safety.

Comment 1-3
Why use the past to report the protocol of a study yet to be performed?
Response 1-3
The study was started on 30 January, 2019, therefore, we refer to the past in our manuscript, with the exception of the statistical analysis.
We have revised the date of start of this study as reported in the CT.gov.

Page 3, line 45
(from January 2019 to July 2021)
Page 6, line 132
between January 2019 and July 2021.

Comment 1-4
How did Authors prepare placebo? Will patients' masking be granted?
Response 1-4
Placebo is a 5 mL vial contained 5.0 mL of bicarbonated Ringer's solution. Patients were not informed which vial is active or placebo, and, furthermore, the study drug was administered unseen by the subject, in order to ensure that the patient was masked to treatment.

Comment 1-5
Will patients treated with revascularization treatments (i.v. thrombolysis, endovascular treatments) be included in the trial?
Response 1-5
Patients scheduled to undergo revascularization treatment including carotid endarterectomy, stenting, etc. before the end of the evaluation were excluded from the study. However, patients treated with intravenous rt-PA and/or revascularization treatments were allowed to be enrolled in the study, although this condition was not specified as an inclusion criterion.

Reviewer: 2
Comment 2-1
Please define the clinical trial phase, as it is not mentioned on the manuscript nor in the ClinicalTrials.gov registry. It seems that it would be a phase IIA / IIB as it is a first-in-human trial and has a dose-finding design. However, in these conditions, the primary endpoint should also concern safety matters. It is remarkable that there is no mention in the introduction section regarding possible adverse events with these cells in ischemic stroke pre-clinical studies and safety issues regarding cell therapy with other cell types in human stroke clinical trials or with DPSCs in human trials for other conditions other than stroke (if existing).
Response 2-1
Our study is a phase 1/2 trial. This information has been added to the manuscript.
Page 3, line 45
This is a first-in-human, randomized, double-blind, placebo-controlled, multicenter, phase 1/2 clinical trial
Page 4, line 63
This study is a first-in-human, randomized, double-blind, placebo-controlled, phase 1/2 clinical trial
Page 6, line 118
The aims of this phase 1/2 study are

This study consists of three cohorts. In the dose-finding cohorts 1 and 2, safety is evaluated, though this is not mentioned as a primary endpoint. Primary and secondary endpoints have been set for cohort 3 alone, after confirmation of safety. We have added more information regarding the clinical safety of BM-MSC, pre-clinical efficacy of DPSC, and pre-clinical toxicity of JTR-161 in the introduction.
Page 5, line 84, and 86
Administration of human BM-MSCs was safe and well tolerated in patients with acute ischemic stroke, but no significant clinical improvement was observed.7,8
Page 5, line 96 – 101
Sakai et al.14 reported that human DPSC transplantation into the completely transected spinal cord of adult rats resulted in marked recovery of hind limb locomotor functions, whereas transplantation of human BM-MSC or skin-derived fibroblasts led to substantially less recovery of locomotor function.

Based on a rat stroke model and an in vitro model of ischemia15, human DPSCs are reported to be a better source of cell therapy for ischemic stroke than human BM-MSCs.
Page 6, line 105 – 111
Preclinical toxicological study of a single intravenous administration of JTR-161 to male and female nude rats showed no notable toxicological findings two weeks after administration (In house data). There were no notable findings regarding tumorigenicity 16 weeks after administration. Furthermore, no scaffold-independent proliferation ability was observed. Regarding non-cellular components of the study product and impurities derived from the manufacturing process, because the amount of residual impurities was low, there were negligible concerns regarding safety.

Comment 2-2
In the study design section, authors mention that a Data and Safety Monitoring Board (DSMB) recommend advancing to the next cohort only when there are no product-related serious adverse events, including 2 or more deaths in a cohort. However, deaths due to cerebral infarction including concomitant symptoms or due to pretreatment with rt-PA and/or endovascular treatment are excluded as causes of death in this sense. Please specify what symptoms are considered by the authors as "concomitant symptoms" in ischemic stroke, in particular if pulmonary infections or other systemic infections are included in this consideration. This point must be clarified, especially as this is the first in-human trial using this cell type and authors mention the fact that this cell type exerts more potent immunosuppressive effects than BM-MSCs.
Response 2-2
We consider transtentorial herniation, followed in frequency by pneumonia, cardiac causes, and pulmonary embolism as a concomitant disorders in ischemic stroke. This has been added in the text to improve clarity. The risk of fatal infections including progressive multifocal leukoencephalopathy, pulmonary infections or other systemic infections cannot be ruled out due to the potent immunosuppressive effects pointed out by the reviewer. However, so far there have not been any reports describing a potential risk of infection caused by cell therapy. If these are observed, they should be recorded as a product-related adverse event.
Page 6, line 126 - 127
Death due to cerebral infarction itself and concomitant disorders including transtentorial herniation, followed in frequency by pneumonia, cardiac causes, and pulmonary embolism, pretreatment with intravenous recombinant tissue-type plasminogen activator (rt-PA) or endovascular treatment, and combination treatment for the primary disease are excluded as causes of death in this study.

Comment 2-3
Comparing information from the study protocol manuscript and information available in Clinical Trials.gov the actual recruitment state and estimated trial initiation and study end dates do not seem clear. Please clarify if all patients have already been included and are currently in follow-up period.
Response 2-3
All patients have already been enrolled. The last enrolled patient was under observation as of 30 October 2020.

Comment 2-4
On the first line of the introduction, the authors mention that "stroke is the most prevalent cerebrovascular disease worldwide, and still one of the leading causes of death and disability", however, the cited reference only refers to Japan and is outdated (published in 2013, refers to epidemiological studies performed more than 10 years ago).
Response 2-4
An updated reference describing the global epidemiology of stroke has been added as a citation.
Page 20, line 443 - 444
2. Lindsay MP, Norrving B, Sacco RL, et al. World Stroke Organization (WSO): Global Stroke Fact Sheet 2019. Int J Stroke. 2019;14:806-17.

Comment 2-5
Concerning inclusion/exclusion criteria: if reperfusion therapies are administered, is there a pre-defined time-point after these therapies in which screening NIHSS will be performed (considering that there could be a significant improvement in neurological function). If so, please specify in the manuscript. Also, is drug or alcohol abuse permitted? This is a usual exclusion criteria in stroke clinical trials.
Response 2-5
We did not set a pre-defined time point after reperfusion therapies. However, a change in NIHSS score from screening ≥5 was excluded from our study as mentioned on pages 10–11, lines 202 – 209.

Comment 2-6
Could the authors explain the reason for including penumbra region volume in exploratory analysis? This imaging parameter does not seem to be very relevant in this clinical trial, as the hypothetic mechanism of action of the DPSCs is not related to reperfusion and no further perfusion measurements are made after the pre-dosing time-point.
Response 2-6
DPSC does not affect reperfusion and improvements in blood flow, therefore, for example, the volume of the penumbra region was not evaluated in the AMASCIS-02 study. However, DPSCs and AD-MSCs should be viable in the penumbra region and may be expected to improve reperfusion and blood flow indirectly. Therefore, we decided to measure penumbra region volume as an exploratory endpoint.

Comment 2-7
Concerning “Procedures”:
2-7-1 Apart from the DPSCs, what other components are present in the study product (excipients)? Which are the components of the placebo solution?
Response 2-7-1
Placebo is a 5 mL vial contained 5.0 mL of bicarbonated Ringer's solution. JTR-161 consists of allogeneic human DPSCs and excipients, which cannot be disclosed.

2-7-2 It would be interesting to have a basal pre-stroke BI assessment, particularly if it will be part of the primary endpoint. Can the authors explain the reason for not performing this measurement?
Response 2-7-2
We evaluate mRS before the onset of stroke. The mRS is evaluated on Day 31, Day 91, Day 366, and the day of discharge. Measuring BI may be acceptable, but we think mRS is sufficient for evaluating the clinical efficacy of JRT-161.

Comment 2-8
In the “Outcome measures” section:
2-8-1 Safety assessments should be included in the primary endpoint, considering the first-inhuman condition of this study.
Response 2-8-1
We did not set safety as a primary endpoint; however, safety is a principal concern in cohorts 1 and 2, before entering the next cohort 3. The primary endpoint regarding efficacy of JRT-161 was set in cohort 3 alone, which can be evaluated after safety of JRT-161 is confirmed. Therefore, we did not set safety as a primary endpoint.

2-8-2 Please clarify if the difference between the secondary endpoint (5) and the primary endpoint is that it includes patients from cohorts 1 and 2 in addition to cohort 3.
Response 2-8-2
The primary endpoint is evaluated in cohort 3 alone. The secondary endpoints are evaluated in cohort

3, and in all cohorts including cohorts 1 and 2.

2-8-3 Consider renaming secondary endpoint (6) "excellent outcome" (mRS <2, improvement in NIHSS >75% and BI > 95) as it may be confused easily with the study primary endpoint and secondary.
Response 2-8-3
We have revised "excellent outcome" with "overall improvement" as shown on the CT. gov website.
Page 14, line 289
Before; (6) proportion of patients who achieve an excellent outcome
After; (6) proportion of patients who achieve overall improvement

Comment 2-9
Sample size estimates: could the authors please explain the method for calculating sample size.
Response 2-9
Our study is an exploratory study, and no efficacy information is available from patients. Therefore, we set a number sufficient for designing a future clinical trial based on the safety and efficacy data.

Comment 2-10
“Study organization and funding” section: Contact data of the sponsor should appear on the manuscript, on this section or on the title page. Also, the role of study sponsors and funders in the decision to submit results for publication should be specified.
Response 2-10
We have revised the study organization and funding section.
Page 16, line 339–345
Teijin Pharma Ltd., Tokyo, Japan and JCR Pharmaceuticals Co., Ltd., Kobe, Japan were involved in study design, data collection, data analysis, data interpretation, writing of the clinical study report, and made the decision to submit the study results for publication. The delegates of the sponsor are Ken-ichi Umino, Teijin Pharma Limited, Clinical Development Department, Research, Development & Technology Unit, 2-1 Kasumigaseki 3-chome, Chiyoda-ku, Tokyo 100-8585, Japan and Kiwamu Imagawa, JCR Pharmaceuticals Co., Ltd., Research Division, Drug Discovery Research Institute, 2-2-9 Murotani, Nishi-ku, Kobe, Hyogo, 651-2241 Japan. This study and its publication are funded by Teijin Pharma Ltd. and JCR Pharmaceuticals Co., Ltd.

Comment 2-11
“Ethics and dissemination”: Protocol date and approved version should be mentioned in this section.
Response 2-11
Protocol date and approved version have been added in this section.
Page 17, line 354– 355
First approval was obtained from the institutional review board of Nippon Medical School on 20 December 2018. The protocol version 02 issued on 2 November 2018 was reviewed there.

Editor(s)' Comments to Author:
Comment 1
Please ensure the Japanese Clinical Trial registration details are shown along with the CT.gov details.
Response to 1
The Japanese Clinical Trial registration details are attached as well as the CT.gov registration, as supplementary files for Editors only. Information about clinical trial registration including the Japanese Clinical Trial registration and CT. gov have been added in the abstract and study design section.
Page 3, line 59
JapicCTI-194570 and Clinical Trials. gov: NCT04608838
Page 7, line 133 - 134
The study was registered as JapicCTI-194570, prior to study patient enrollment, and subsequently on

Clinical Trials.gov: NCT04608838.

Comment 2
Along with your revised manuscript, please provide an example of the patient consent form as a supplementary file as per item #32 of the SPIRIT checklist.
Response to 2
An original example of the patient consent form written in Japanese and an English translation are attached as a supplementary files for Editors only. If the English version of the content form does not conform to the Japanese versions, the Japanese version shall prevail.

Comments by e-mail dated 28-Dec-2021 Subject: BMJ Open - bmjopen-2021-054269.R1 requires your attention

Comment 1
Please provide figure legend before reference list.
Response to 1
Figure legend has been added.
Page 19-20, line 437 and 439
Figure 1 Flow chart of the cohorts
DSMB, Data and Safety Monitoring Board

Comment 2
Please provide table in editable format.
Response to 2
Table 1 is attached in excel.

Comment 3
It was checked that you have uploaded the below files under supplementary material but missing citations within the main text:
Informed consent form_Japanese.pdf
Informed consent form_English.pdf
JapicCTI.pdf
ClinicalTrials.gov.pdf
Please ensure to cite this as supplementary file (ie, supplementary file_Informed consent form_Japanese). However, if these files are for editors only, please upload this under ' Supplemental Material for Editors only'.
Response to 3
These files are attached as a supplementary files for Editors only.

Others
Acknowledgement has been added.
Page 19, line 415 and 416
The authors thank Ken-ichi Umino, Teijin Pharma Limited and Kiwamu Imagawa, JCR Pharmaceuticals Co., Ltd. for supporting the study design.

One reference has been added.
Page 21, line 480 - 482
15. Song M, Lee JH, Bae J, Bu Y, Kim EC. Human dental pulp stem cells are more effective than human bone marrow-derived mesenchymal stem cells in cerebral ischemic injury. Cell Transplant. 2017;26:1001-16.

One reference has been changed to an alternate adequate one.

Page 21, line 474 – 476
13. Sugiyama M, Iohara K, Wakita H, et al. Dental pulp-derived $CD31^{-}/CD146^{-}$ side population stem/progenitor cells enhance recovery of focal cerebral ischemia in rats. Tissue Eng Part A. 2011;17:1303-11.

More details regarding study registration have been described.
Page 3, line 59
Trial registration: JapicCTI-194570 and Clinical Trials. gov: NCT04608838
Page 7, line 133 and 134
The study was registered as JapicCTI-194570, prior to study patient enrollment, and subsequently on Clinical Trials.gov: NCT04608838.

VERSION 2 – REVIEW

REVIEWER	de Celis-Ruiz, Elena La Paz University Hospital Biomedical Research Foundation
REVIEW RETURNED	21-Jan-2022

GENERAL COMMENTS	The authors have answered the questions raised and clarified most points in the manuscript. However, there are some minor matters that still need further clarification. 1. “Methods and Analysis; study design” section, sentence on lines 126-130: “Death due to cerebral infarction itself and concomitant disorders including transtentorial herniation, followed in frequency by pneumonia, cardiac causes, and pulmonary embolism, pretreatment with intravenous recombinant tissue-type plasminogen activator (rt-PA) or endovascular treatment, and combination treatment for the primary disease are excluded as causes of death in this study” This sentence still needs more clarification; it is difficult to understand as it is written. Do the authors mean that only unexpected deaths (those not considered related to ischemic stroke or its most frequent complications, or related to acute reperfusion treatments such as rt-PA or endovascular procedures) will be considered a security breach sufficient for preventing advance to the next cohort (in addition to other safety concerns)? I understand that the authors consider transtentorial herniation, pneumonia and pulmonary embolism potential complications in stroke patients and I agree with this point, though death due to pneumonia is probably more frequent than death due to transtentorial herniation; consider rephrasing this. 2. “Methods and Analysis; procedures” section., line 245. Is there a particular reason why “start time” is only registered for endovascular treatment and not for rt-PA? 3. “Methods and Analysis; outcome measures” section., line 282-289. -Please clarify that secondary endpoint 5 refers to all of the patients, including cohorts 1 and 2. - I do not understand the reason why the description of EQ-5D-5L scale is mentioned after secondary endpoint 5 description, as it does not take part of the “excellent outcome” definition.

	4. “Methods and Analysis; statistical analyses”; line 310 “Efficacy analyses will be performed in the full analysis set (FAS); the population of enrolled patients who will have received the study product at least once and have had a post-dose efficacy assessment…”. Consider rephrasing this; it could be interpreted as if patients can receive treatment with iv JTR-161 more than once and by protocol authors mention that a single iv dose is administered to each patient.

VERSION 2 – AUTHOR RESPONSE

Reviewer #2

Dr. Elena de Celis-Ruiz, La Paz University Hospital Biomedical Research Foundation

Comments to the Author:

The authors have answered the questions raised and clarified most points in the manuscript. However, there are some minor matters that still need further clarification.

1. “Methods and Analysis; study design” section, sentence on lines 126-130: “Death due to cerebral infarction itself and concomitant disorders including transtentorial herniation, followed in frequency by pneumonia, cardiac causes, and pulmonary embolism, pretreatment with intravenous recombinant tissue-type plasminogen activator (rt-PA) or endovascular treatment, and combination treatment for the primary disease are excluded as causes of death in this study.This sentence still needs more clarification; it is difficult to understand as it is written. Do the authors mean that only unexpected deaths (those not considered related to ischemic stroke or its most frequent complications, or related to acute reperfusion treatments such as rt-PA or endovascular procedures) will be considered a security breach sufficient for preventing advance to the next cohort (in addition to other safety concerns)? I understand that the authors consider transtentorial herniation, pneumonia and pulmonary embolism potential complications in stroke patients and I agree with this point, though death due to pneumonia is probably more frequent than death due to transtentorial herniation; consider rephrasing this.

Response to #2-1

As you pointed out, the deaths should be considered as a serious safety concern for advancing to the next cohort when product-related death or death for which a causal relationship cannot be ruled out occur. We have revised the text.

Page 6, line 122 - 128

The DSMB consists of three independent external experts. ~~and recommends advancing to the next cohort only when no product-related serious adverse events (AEs) are observed~~ The DSMB does not recommend advancing to the next cohort when two or more product-related death or death for which a causal relationship cannot be ruled out occur in the same cohort, or any other serious safety concerns are reported. Death due to cerebral infarction itself and concomitant disorders including pneumonia and transtentorial herniation, followed in frequency by ~~pneumonia,~~ cardiac causes and pulmonary embolism,

2. “Methods and Analysis; procedures” section., line 245.
   Is there a particular reason why “start time” is only registered for endovascular treatment and not for rt-PA?

Response to #2-2

Thank you for bringing this error to our attention. In both endovascular treatment and rt-PA, start time was required to be recorded. Therefore,” (endovascular treatment only)” has been removed.

Page 13, line 245 – 246

If yes, treatment start time ~~(endovascular treatment only)~~ ...

3. “Methods and Analysis; outcome measures” section., line 282-289.
   -Please clarify that secondary endpoint 5 refers to all of the patients, including cohorts 1 and 2.

- I do not understand the reason why the description of EQ-5D-5L scale is mentioned after secondary endpoint 5 description, as it does not take part of the “excellent outcome” definition.

Response to #2-3

The secondary endpoint 5 was evaluated in all patients in the cohort 1 and 2.
The place of this sentence was wrong. We have changed the sentence in the proper position.
Page 14, 15, line 291 -297

4. “Methods and Analysis; statistical analyses”; line 310 “Efficacy analyses will be performed in the full analysis set (FAS); the population of enrolled patients who will have received the study product at least once and have had a post-dose efficacy assessment…”.
   Consider rephrasing this; it could be interpreted as if patients can receive treatment with iv JTR-161 more than once and by protocol authors mention that a single iv dose is administered to each patient.

Response to #2-4

Thank you for bringing this error to our attention. We have removed “at least” from the text.
Page 15, line 317
... who will have received the study product ~~at least~~ once ...