

Clinical study protocol

A Double-Blind, Randomized, Placebo-Controlled Study of
GB-0998 in Patients with Unexplained Recurrent Miscarriage.

Sponsor: Japan Blood Products Organization

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Confidentiality Statement

This clinical study protocol contains information that is provided only to those directly involved in the study. Before disclosing the contents of this protocol to the public or to a third party, please obtain prior written consent from the Japan Blood Products Organization.

Protocol Summary

Study objectives	The objective is to demonstrate the efficacy of GB-0998 in the treatment of unexplained recurrent miscarriage based on the continuing rate of pregnancy at 22 weeks of gestation as the primary endpoint in comparison to placebo using a multicenter, double-blind, intergroup comparison method. The safety of GB-0998 will also be evaluated.
Target disease	Unexplained Recurrent Miscarriage Among the patients whose risk factors for recurrent miscarriage are unknown who repeatedly miscarry or patients who repeatedly miscarry despite treatment for risk factors, those who meet the following inclusion criteria and do not meet any of the exclusion criteria are eligible for this study.
Inclusion criteria	<p>(1) Patients with primary recurrent miscarriage</p> <p>(2) Patients with a history of at least 4 miscarriages (not including biochemical pregnancy in the count of prior miscarriages)</p> <p>(3) Patients with any of the following risk factors for recurrent miscarriage</p> <ul style="list-style-type: none"> ● Patients with unknown risk factors <ul style="list-style-type: none"> Patients with normal test results for each of the following risk factors who have experienced miscarriage of a fetus with normal chromosome karyotype <ol style="list-style-type: none"> 1) Abnormal uterine morphology* 2) Thyroid dysfunction 3) Chromosome abnormality in the couple 4) Positive antiphospholipid antibody** 5) Factor XII deficiency*** 6) Protein S deficiency*** 7) Protein C deficiency*** <div style="border: 1px dashed black; padding: 5px; margin: 10px 0;"> <p>* An arcuate uterus will not be considered a risk factor.</p> <p>** This refers to patients who meet the diagnostic criteria for antiphospholipid syndrome and patients with incidentally positive antiphospholipid antibody (see Appendix 6).</p> <p>*** Determined by the investigator based on the results of measurement or the result of diagnosis, at the study site or another medical institution.</p> </div> ● Patients determined to have risk factors <ul style="list-style-type: none"> Patients with the following risk factors who have experienced miscarriage of a fetus with normal chromosome karyotype despite receiving treatment for these factors <ol style="list-style-type: none"> 1) Abnormal uterine morphology (septate uterus): Patients who have undergone surgery 2) Thyroid dysfunction: Patients receiving medical treatment 3) Incidentally positive antiphospholipid antibody (see Appendix 6; however, the latest test result should be negative), factor XII deficiency, protein S deficiency, protein C deficiency: Patients receiving combination therapy with aspirin and heparin <p>(4) Regardless of whether or not risk factors are present, patients should have experienced at least 1 a miscarriage of a fetus with normal chromosome karyotype</p> <p>(5) Patients below the age of 42 years at the time of obtaining informed consent</p> <p>(6) Patients who can be admitted for at least the period from the start date of administration of the study drug to the date of examination and assessment 1 week after the start of administration of the study drug</p> <p>(7) Patients who have given written informed consent to participate in this study</p>

Exclusion criteria	<p>(1) Patients with chromosome abnormalities in themselves or their partners that are risk factors for recurrent miscarriage, patients with antiphospholipid syndrome, and patients with incidentally positive antiphospholipid antibody (when the latest test result is positive)****</p> <p>(2) Patients in whom complications of diabetes mellitus or impaired glucose tolerance has been identified, but who have not received appropriate treatment for this condition</p> <p>(3) Patients who have received intravenous immunoglobulin therapy as treatment for recurrent miscarriage in the past</p> <p>(4) Patients with a history of stillbirth at 22 weeks of gestation or later</p> <p>(5) Patients receiving treatment for malignant tumor</p> <p>(6) Patients with a history of thromboembolism</p> <p>(7) Patients with a history of shock or hypersensitivity in response to the ingredients of this drug or patients with hereditary fructose intolerance</p> <p>(8) Patients who have been diagnosed with IgA deficiency in the past or patients who have a serum IgA level of <5 mg/dL at laboratory tests at registration</p> <p>(9) Patients who have received another study drug within the period of 12 weeks prior to informed consent or who are currently participating in another clinical trial</p> <p>(10) Patients who are unsuitable for this study for any other reason, in the opinion of a principal investigator or sub-investigators</p> <p style="text-align: center;">**** See Appendix 6 for information on antiphospholipid syndrome and incidentally positive antiphospholipid antibody.</p>
Study design	Multicenter, double-blind, group-comparison study (stratified randomization)
Investigational product	<p>Name of investigational products</p> <ul style="list-style-type: none"> ● Investigational product : GB-0998 ● Control drug : saline <p>Dosage form and strength</p> <ul style="list-style-type: none"> ● GB-0998 : each vial (50 mL) contains 2,500 mg of normal human immunoglobulin G solution for injection ● Placebo : each vial (50 mL) contains 450 mg of sodium chloride solution for injection (saline) <p>Packaging form</p> <p>Each vial of investigational product (GB-0998 or placebo) is placed in an individual package carton, and each carton is placed in an outer carton containing 10 individual package cartons.</p>
Dosage and administration	<p>Either GB-0998 or placebo will be administered once daily at a dose of 8 mL/kg body weight by intravenous infusion for 5 consecutive days. Administration of this product should be started after confirmation of the gestational sac by ultrasonography (from Week 4 Day 0 to Week 6 Day 6 of gestation). The number of weeks of gestation should be calculated based on obstetrically reasonable criteria, such as the last menstrual period, basal body temperature, and date of embryo transfer, and any of the calculation results being within the specified range is sufficient. The daily dose is the dose specified in the enrollment confirmation sheet.</p>

Concomitant medications	<p>Prohibited concomitant medications The following medications are prohibited from the time of informed consent until miscarriage/stillbirth, delivery, or discontinuation.</p> <ol style="list-style-type: none"> 1) Normal human immunoglobulin preparations other than the investigational product 2) Whole blood preparations 3) Fresh frozen human plasma 4) Other investigational products <p>Restricted concomitant medications Administration of antithrombotic drugs such as aspirin and heparin and corticosteroids for treatment of recurrent miscarriage is allowed if the patient experienced a miscarriage of an infant with normal fetal chromosomes and treatment was confirmed to be ineffective, but the dose should not be increased until 22 weeks of gestation (however, this does not apply to minor dose adjustments for safety and dose modifications for low-dose aspirin therapy).</p> <p>In addition, in patients with concomitant autoimmune diseases such as systemic lupus erythematosus (SLE), continuation of treatment is allowed if the patient has received corticosteroids for the treatment of autoimmune diseases and has had a subsequent miscarriage of an infant with normal fetal chromosomes.</p>
Observation, test, and survey items along with timing(Schedule)	Refer to Figure 1
Evaluation items	<p>Primary endpoint of efficacy Ongoing pregnancy rate at 22 weeks of gestation (excluding miscarriages associated with fetal chromosomal abnormalities)</p> <p>Secondary endpoint of efficacy</p> <ul style="list-style-type: none"> ● Ongoing pregnancy rate at 22 weeks of gestation (all patients) ● Rate of live births (excluding miscarriages associated with fetal chromosomal abnormalities) ● Rate of live births (all patients) <p>Safety</p> <ul style="list-style-type: none"> ● Laboratory tests (Hematology, blood biochemistry, immunology, urinalysis) ● Ultrasonography (Fetal findings: crown-rump length, biparietal diameter, femur length, presence/absence of abnormalities) ● Observations during delivery or miscarriage/stillbirth (Findings at birth, findings in newborns, miscarriage/stillbirth findings) ● Adverse events
Study period	The study period will be from informed consent to discharge after childbirth or after miscarriage/stillbirth.
Target sample size	<p>The number of patients in a group was set to be 40 as the target number of patients for efficacy evaluation (the number of patients excluding miscarriages due to fetal chromosomal abnormalities)</p> <ul style="list-style-type: none"> ● Number of previous miscarriages: ≥ 6 : ≥ 10 per group ● Number of previous miscarriages: 4, 5 : ≤ 30/group
Clinical study period	February 2014 to June 2021

Figure 1. Observation, test, and survey items along with timing

Item	Prior to start	Hospitalization period							1 week after start of administration Day 8 ⁶⁾	Observation of course of pregnancy ⁷⁾							
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		8 weeks of gestation	12 weeks of gestation	16 weeks of gestation	20 weeks of gestation	22 weeks of gestation	28 weeks of gestation	32 weeks of gestation	36 weeks of gestation
Timing																	
Obtain informed consent	•																
Confirmation of demographics	•																
IgA ¹⁾	•																
Body weight	•																
Confirmation of fetal sac ²⁾	•																
Patient enrollment ³⁾	•																
Laboratory tests ⁴⁾		•							•	•		•		•			
Administration of investigational product ⁵⁾			•	•	•	•	•										
Ultrasonography									•	•	•	•	•	•	•	•	
Findings at birth																	•
Findings in newborns																	• ⁸⁾
Miscarriage/stillbirth findings																	• ⁹⁾
Adverse events																	

Clinical laboratory tests

Hematology Red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Ht), white blood cell (WBC) count, WBC differential [neutrophils (Neut), lymphocytes (Lym), monocytes (Mono), eosinophils (Eos), basophils (Baso)], platelet (Plt) count, D-dimer¹⁰⁾

Blood biochemistry Total protein (TP), albumin (Alb), aspartate transaminase (AST/GOT), alanine transaminase (ALT/GPT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-GTP, blood urea nitrogen (BUN), creatinine (CRE), uric acid (UA), sodium (Na), potassium (K), chloride (Cl), C-reactive protein (CRP)

Immunology Immunoglobulin G (IgG), natural killer (NK) cell activity¹¹⁾, Tregs¹¹⁾

Urinalysis Protein, glucose, urobilinogen

Ultrasonography Fetal findings: crown-rump length, transverse diameter, femur length, presence/absence of abnormalities

Findings at birth Number of weeks, method of delivery (vaginal delivery, cesarean section)

Findings in newborns Infant weight, Apgar score (1 min, 5 min), presence/absence of abnormalities

Miscarriage/stillbirth findings Number of weeks, karyotype analysis findings

- 1) Measurements will be performed at the study site or at the central laboratory only prior to enrollment (if past data at other hospitals, etc. are available, re-measurement is not necessary).
- 2) The gestational sac will be confirmed by ultrasonography prior to enrollment.
- 3) After informed consent is obtained, participants will be enrolled by 5 weeks and 6 days of gestation after confirmation of eligibility based on inclusion and exclusion criteria.
- 4) Laboratory tests will be performed not only at the time points shown in the figure above but also at the time of miscarriage (not necessary if miscarriage occurs prior to the start of investigational product administration) and at the time of discontinuation before 22 weeks of gestation.
- 5) The start date of treatment with investigational product is between 4 weeks 0 days and until 6 weeks 6 days of gestation after confirmation of the gestational sac by ultrasonography. The number of weeks of gestation should be calculated based on obstetrically reasonable criteria, such as the last menstrual period, basal body temperature, and date of embryo transfer, and any of the calculation results being within the specified range is sufficient.
- 6) The allowable range is 1 week ± 1 day after the start of treatment with the investigational product.
- 7) The allowable window for observations during the course of pregnancy is +14 days at 22 weeks of gestation and ±14 days for other time points.
- 8) This will be monitored until discharge.
- 9) If a miscarriage/stillbirth occurs, karyotyping will be performed (not required if the miscarriage occurs prior to starting investigational product).
- 10) Measurements will be performed only prior to the start of administration of investigational product and 1 week after the start of administration. However, if a miscarriage occurs after the start of investigational product administration and prior to the examination 1 week after the start of administration, the test will also be performed as a test at the time of miscarriage.
- 11) This will only be measured prior to the start of treatment with investigational product, 1 week after the start of treatment with investigational product, and at 8 weeks of gestation. However, if a miscarriage occurs after the start of investigational product administration and prior to the examination at 8 weeks of gestation, the test will also be performed as a test at the time of miscarriage.

List of abbreviations and definition of terms

Abbreviations and terms used in this clinical study protocol are defined as follows.

Abbreviations	Definition of terms
CIDP	Chronic inflammatory demyelinating polyneuropathy
GBS	Guillain-Barré syndrome
ITP	Idiopathic thrombocytopenic purpura
IVIG	Intravenous immunoglobulin
MG	Myasthenia Gravis
NK	Natural killer (cell)
SLE	Systemic lupus erythematosus
Treg	Regulatory T Cell
VG-IH	Venoglobulin [®] IH

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1. Background (background information leading up to the study)

Recurrent miscarriage is defined as "a condition in which a child cannot be obtained through repeated, at least 2, miscarriages/stillbirths or premature neonatal deaths that occur within 1 week of birth despite pregnancy" ¹⁾. The experience of repeated miscarriages and stillbirths despite pregnancy cause great sadness and stress to women, leading to such consequences as depression and anxiety disorders, and giving up on pregnancy ²⁾, and can be said to be a serious disease for couples who wish to have children. According to a recent Health and Labour Sciences Research, the "Research on re-evaluation of treatment for recurrent miscarriages and development of new treatment methods (Representative researcher: Shigeru Saito, Professor, University of Toyama) (hereinafter, the research group on recurrent miscarriage)," the incidence of recurrent miscarriage was reportedly 4.2% ³⁾. In addition, given that older age at first birth has been pointed out ⁴⁾ and that the risk of miscarriage increases with aging ^{1, 5)}, the inference is that the proportion of patients with recurrent miscarriage tends to increase among those who wish to become pregnant.

The causes are diverse and can be divided into fetal and maternal factors. In early miscarriage (miscarriage <12 weeks gestation) that accounts for the majority of miscarriages, chromosomal abnormalities are frequently observed in fetuses ^{6, 7)}, which was revealed in a survey by the research group on recurrent miscarriage and, from this, it is estimated that many accidental miscarriages caused by chromosomal abnormalities in fetuses are included in recurrent miscarriage. On the other hand, as maternal factors, in addition to psychological factors such as stress and aging, there are known "risk factors" that increase the risk of miscarriage such as uterine morphology abnormality, thyroid abnormality, chromosome abnormalities in the couple, and blood coagulation abnormality ¹⁾. However, according to an investigation by the research group on recurrent miscarriage, 65.3% of patients were found to have no detectable risk factors ¹⁾ and, although the inference is that some of these recurrent miscarriage patients with "unknown risk factors" had an accidental miscarriage caused by the aforementioned fetal chromosomal abnormalities, the assumption is that there were also patients for whom the causes were completely unknown.

Due to the possibility of accidental repeated miscarriages and the possibility of psychological factors, stress reduction through counseling is said to be useful for the treatment of recurrent miscarriages ⁸⁾; however, if recurrent miscarriages still occur, tests for risk factors can be performed and, if risk factors are found, treatment according to the respective risk factors can be administered. Specifically, surgery is considered for some uterine morphological abnormalities, control by a medical specialist is considered for thyroid abnormalities, and anticoagulation therapy with agents such as low-dose aspirin is considered for coagulation abnormalities. In addition, counseling is also provided when chromosome abnormalities are observed in the couple or risk factors are unknown ¹⁾. These therapies are said to eventually lead to successful

births in 85% of all patients with recurrent miscarriage⁹⁾. On the other hand, according to a survey by the research group on recurrent miscarriage, the more prior miscarriages the lower the rate of successful live births even with treatment, suggesting the limitation of existing treatments¹⁰⁾.

Typically, in pregnancy, immune tolerance is induced to prevent rejection of the fetus because the fetus is foreign to the mother; however, in recurrent miscarriage, some abnormalities in this mechanism are considered to have developed^{11, 12)}. Thus, efforts to evaluate the efficacy of intravenous immunoglobulin (IVIG) therapy for recurrent miscarriage, which is known to be effective for various autoimmune diseases such as idiopathic thrombocytopenic purpura (ITP), Guillain-Barre syndrome (GBS), and chronic inflammatory demyelinating polyradiculoneuritis (CIDP), has been conducted for more than 20 years in Japan and overseas. Overseas, there have been 8 reports of placebo-controlled double-blind comparative studies in patients with recurrent miscarriage of unknown cause¹³⁻²⁰⁾; however, clear efficacy has not been confirmed with the exception of 1 report¹⁵⁾. On the other hand, while there have been no reports of double-blind comparative studies in Japan, Yamada et al. reported favorable results in patients with ≥ 4 recurrent miscarriages of unknown cause when 20 g/day was administered for 5 days during early pregnancy²¹⁾. The main differences from reports overseas are that, in the report by Yamada et al., the study was conducted in patients with a relatively high number of prior miscarriages, and drugs were not administered in a dispersed manner during the pregnancy period but were administered intensively during early pregnancy. These aforementioned results suggest that IVIG therapy, if administered intensively during early pregnancy, may be an effective treatment for patients with a high number of recurrent miscarriages of unknown cause.

The mechanism of action of immunomodulatory effects of IVIG therapy are thought to be the normalization of abnormally activated immune cells (NK cells, etc.) at the maternal-fetal interface in patients with recurrent miscarriage^{22, 23)}. In addition, no teratogenicity was observed with human immunoglobulin preparations^{24, 25)} and there were no particular issues with the safety of administration during early pregnancy both in Japan and overseas.

Based on the above, evaluating the efficacy and safety of IVIG therapy in patients with recurrent unexplained miscarriage and a relatively high number of prior miscarriages was considered clinically significant and a Phase III study (multicenter, double-blind, parallel-group study) was planned to evaluate the efficacy and safety of IVIG therapy.

For the preparation of the clinical study protocol, guidance and advice were obtained from the Pharmaceuticals and Medical Devices Agency (PMDA) during a face-to-face consultation meeting.

1.1. Summary of non-clinical studies

(1) Effects on immunity and inflammation

Immunity is a highly regulated biological defense mechanism consisting of complex and diverse chain reactions involving recognition, transmission (presentation), elimination, and tolerance of foreign substances and infected cells. High-dose immunoglobulin therapy is clinically indicated for a wide variety of diseases derived from immune disorders, and has been reported to have immunomodulatory effects. For example, there have been reports of immune-activating effects on neutrophils and complement working against drug-resistant bacteria^{26, 27)}, neutralizing effects against inflammatory cytokines^{28, 29)}, and an immunosuppressive effect on antigens of activated B cells and T cells³⁰⁻³⁵⁾. Phenomena from a pharmacological research perspective that have been reported include activity such as antibodies against the variable region of the antibody (anti-idiotypic antibodies) regulating the blood concentration of specific antibodies^{36, 37)}, the enhancement of expression of inhibitory receptors³⁸⁾, the inhibition of production of autoantibodies³⁹⁾, and the inhibition of complement-dependent cytotoxicity⁴⁰⁾.

(2) Effects in a fetal mouse resorption model

Abortion in recurrent miscarriage has been studied in a mouse fetal resorption model⁴¹⁻⁴³⁾.

The effects of GB-0998 are also currently being investigated using the same model.

An outline of the report from Takeda et al., who evaluated the pharmacological effect of IVIG in a mouse fetal resorption model is shown as a reference⁴⁴⁾. Female CBA/J mice were mated with male DBA/2J mice and pregnant female CBA/J mice were treated with polyinosinic-polycytidylic acid (Poly (I:C)) on gestation day 7.5. IVIG or F(ab')₂ fragments (IgG excluding the Fc region by enzymatic digestion), which were the investigational drugs, were also administered for 3 consecutive days from the same day. Mice were sacrificed on gestation day 13.5, and efficacy was evaluated based on fetal resorption. The results showed that F(ab')₂ fragment administration did not show any efficacy, while IVIG administration significantly decreased the fetal resorption rate compared to the Poly (I:C) monotherapy group. IVIG reportedly may reduce the rate of fetal resorption at sites other than the variable regions in the fetal resorption model in mice.

1.2. Summary of clinical studies

No clinical studies of GB-0998 in recurrent miscarriage have been conducted prior to this clinical study.

The summary of the report by Yamada et al. in Japan among clinical research on IVIG therapy for recurrent miscarriage is shown below. In addition, an outline of overseas reports showing the efficacy in placebo-controlled double-blind comparative studies, which are different from the report by Yamada et al. and the protocol for this study, is presented.

Yamada et al.²¹⁾ administered IVIG therapy to 60 patients with a history of ≥ 4 spontaneous abortions of unknown cause based on various tests. As IVIG therapy, immunoglobulin 20 g/day was administered consecutively for 5 days (total dose 100 g) immediately after the fetal sac was confirmed by ultrasonography. Of the 60 patients, 44 resulted in live birth, 1 resulted in fetal death at 31 weeks of gestation and 15 resulted in miscarriage. Chromosomal karyotype analysis of the villous cells confirmed fetal chromosomal abnormalities in 11 of the miscarriages. Based on this result, the live birth rate was 73.3% (44/60), and the live birth rate was 89.8% (44/49) when miscarriages due to fetal chromosome abnormalities for whom the evaluation of therapeutic effects could not be made were excluded.

Coulam et al.¹⁵⁾ randomized 95 patients with unexplained recurrent miscarriages who had 2 or more previous miscarriages to 2 groups (the IVIG arm and placebo arm). The doses were 500 mg/kg body weight in the IVIG arm and 0.5% albumin in the placebo arm, during the follicular phase of the desired month of pregnancy, and dosing was repeated every 28 days until pregnancy or up to 4 months. For those who became pregnant, administration was every 28 days until delivery or 28 to 32 weeks of gestation. Of the 61 patients (29 IVIG, 32 placebo), excluding the 34 who did not become pregnant, the live birth rate was significantly higher in the IVIG arm: 62.1% (18/29) in the IVIG arm and 34.4% (11/32) in the placebo arm ($p=0.04$).

2. General principles

This study will be conducted while respecting the spirit of the Declaration of Helsinki, and in compliance with the Pharmaceutical and Medical Devices (PMD) Act, Good Clinical Practice (GCP), and related laws and regulations.

3. Clinical study administrative structure

3.1. Sponsor

(1) Name and address of the sponsor

Japan Blood Products Organization

7th floor World Trade Center Building, 2-4-1 Hamamatsucho, Minato-ku, Tokyo
105-6107

(2) Responsible individual at the sponsor

Hiroyuki Ishikawa, Director of Clinical Operation Development Department, Research and Development Division, Japan Blood Products Organization

7th floor World Trade Center Building, 2-4-1 Hamamatsucho, Minato-ku, Tokyo
105-6107

Telephone no.: 03-6435-6515 Fax no.: 03-3436-2933

[Business activities]

Overall responsibility for activities related to the request and management of the clinical study

(3) Medical expert

Hideto Yamada (Department of Obstetrics and Gynecology, Kobe University Graduate School of Medicine)

7-5-2 Kusunoki-cho, Chuo-ku, Kobe-city, Hyogo 650-0017

Telephone no.: 078-382-5111

Yasuhiro Yamamoto (Advisor, Japan Blood Products Organization)

7th floor World Trade Center Building, 2-4-1 Hamamatsucho, Minato-ku, Tokyo
105-6107

Telephone no.: 03-6435-6515 Fax no.: 03-3436-2933

[Main business activities]

To provide advice from a medical standpoint on the following matters to be conducted by the sponsor:

- [1] Preparation and revision of the protocol, case report form (sample), and Investigator's Brochure (IB)
- [2] Contents of the written information and the informed consent form (draft)
- [3] Principal investigator and study site selection
- [4] Selection of a coordinating investigator, as needed
- [5] Medical assessment of individual patients

- [6] Assessment and handling of investigational product safety information
- [7] Preparation of the clinical study report
- [8] Handling of other matters related to the study not expected at the start of the study

(4) Individual responsible for project management

Refer to the administrative structure list (Appendix 1)

[Main business activities]

Responsible for supervising the clinical study group and the contract research organizations in charge of preparing the protocol for the clinical study, requesting participation in the clinical study, monitoring the clinical study, summarizing the results of the clinical study, and preparing a clinical study report, and executing activities

(5) Monitor

Refer to the administrative structure list (Appendix 1)

[Main business activities]

Confirm that the human rights, safety, and welfare of study participants are protected, that the study is being conducted in compliance with the latest protocol, GCP, etc., and that the study data are accurate, complete, and verifiable from the study-related records such as source documents

(6) Responsible auditor

Refer to the administrative structure list (Appendix 1)

[Main business activities]

Confirm appropriate conduct of audit activities

3.2. GB-0998 (Recurrent miscarriage) registration center

EPS Corporation

Acropolis Tokyo, 6-29 Shinogawamachi, Shinjuku-ku, Tokyo 162-0814

Telephone no.: 03-5684-7707

[Main business activities]

Accept enrollment of patients from principal investigators (or sub-investigators) based on the Service Agreement and, if there are any inadequacies in the enrollment information, perform enrollment of patients and manage enrollment information such as confirming the contents with the enrolling physician

3.3. Central laboratory

(Outsourcing contact)

SRL MediSearch Inc.

Shinjuku i-LAND Tower 10 F, 6-5-1 Nishishinjuku, Shinjuku-ku, Tokyo
163-1310

Telephone no.: 03-5324-2602

(Sample measurement)

SRL, Inc.

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

Telephone no.: 03-6279-0900

[Main business activities]

Perform the duties and functions associated with laboratory testing and reporting in accordance with the laboratory procedures and Service Agreement

3.4. Study sites and principal investigators

Refer to the list of study sites and investigators (Appendix 2).

[Main activities of the principal investigator]

Agreement on the protocol prepared by the sponsor, preparation and revision of the written information and informed consent form, selection of study participants and obtainment of consent, conduct of the study, provision of medical care and information to study participants, guidance and supervision of sub-investigators and study collaborators, provision of materials and information, cooperation in monitoring and audits, reporting of protocol deviations or changes and adverse events, preparation of case report forms (CRFs), and archiving of essential documents

3.5. Coordinating investigator

Shigeru Saito (Department of Obstetrics and Gynecology, University of Toyama)

2630 Sugitani, Toyama-shi, Toyama, 930-0194

Telephone no.: 076-434-2281

[Main business activities]

Provide advice, as necessary, to the sponsor as a specialist in the field of this study, on activities related to the coordination of study sites in a multicenter study, such as the review of the protocol, coordination of study sites regarding details in the protocol, and doubts arising during the study concerning the interpretation of the protocol

3.6. Supervisors in statistical analysis

Biomet Corporation

Katsuyuki Haino (President)

Forest Ochyanomizu 301, 1-10-5 Yushima, Bunkyo-ku, Tokyo 113-0034

Telephone no.: 03-6801-5166

[Main business activities]

Supervision of the entire analysis plan, including the analysis work outsourced to the CRO, and implementation of additional analysis as necessary

3.7. Investigational product randomization manager

EPS Corporation, Patient registration center

Shigeru Hishiyama

Acropolis Tokyo, 6-29 Shinogawamachi, Shinjuku-ku, Tokyo 162-0814

Telephone no.: 03-5684-7707

[Main business activities]

Preparation and management of key codes, allocation of medication, confirmation of the indistinguishability of the appearance and packaging of investigational product, preparation of emergency keys and unblinding based on the sponsor's decision, breaking key codes, and confirmation of the blinding of investigational product until key code breaking

3.8. Contract research organizations

(1) Monitoring activities

Refer to the administrative structure list (Appendix 1)

[Main business activities]

Perform monitoring activities in accordance with the Service Agreement

(2) Data management activities

Refer to the administrative structure list (Appendix 1)

[Main business activities]

Perform data management activities in accordance with the Service Agreement

(3) Statistical analysis activities

Refer to the administrative structure list (Appendix 1)

[Main business activities]

Perform statistical analysis activities in accordance with the Service Agreement

(4) Investigational product storage and transport activities

Refer to the administrative structure list (Appendix 1)

[Main business activities]

Perform investigational product storage and transport activities in accordance with the Service Agreement

3.9. Contract audit organization

Refer to the administrative structure list (Appendix 1)

[Main business activities]

Evaluate whether the clinical study is being conducted in accordance with the protocol, the administrative instructions on sponsoring and managing the clinical study, the standard operating procedures in the GCP, the standards specified in Article 14, Paragraph 3 and Article 80-2 of the Pharmaceuticals and Medical Devices (PMD) Act, and GCP as part of quality assurance of the clinical study, independently and separately from routine monitoring and clinical study quality control activities, based on the Service Agreement

4. Study objectives and design

4.1. Study objectives

The objective is to demonstrate the efficacy of GB-0998 in the treatment of unexplained recurrent miscarriage based on the continuing rate of pregnancy at 22 weeks of gestation as the primary endpoint in comparison to placebo using a multicenter, double-blind, inter-group comparison method. The safety of GB-0998 will also be evaluated.

4.2. Study type

- (1) Phase of development: Phase III
- (2) Study type: Confirmatory study

4.3. Study design

(1) Study method

Multicenter, double-blind, group-comparison study (stratified randomization)

(2) Stratified randomization and group composition

- 1) Patients will be randomly assigned to either 4 or 5 previous miscarriages or ≥ 6 previous miscarriages
- 2) Composition of treatment groups
 - GB-0998 group
 - Placebo group (saline administration)

(3) Equalization of age

Patients will be equally randomized to both treatment groups using the minimization method with age (≥ 35 years and < 35 years) as an allocation adjustment factor.

[Rationale for setting]

Since the only report in Japan and overseas suggesting the efficacy of IVIG therapy in the dosage and administration of this study was from Yamada et al. (open-label study), a placebo (physiological saline) group was included in the study to verify the efficacy of this method.

According to the report on the rate of live births by the number of previous miscarriages by the research group on recurrent miscarriages, there was a difference in the live birth rate between patients with a history of 6 or more miscarriages versus patients with 4 or 5 miscarriages. Patients with ≥ 6 previous miscarriages were stratified by the number of previous miscarriages in both groups since these patients had repeated miscarriages after undergoing adequate tests and treatments in the past and may be less responsive to treatment compared to patients with < 6 previous miscarriages. In addition, since it is known that aging decreases the rate of live births, a decision was made to equally randomize between the ages of ≥ 35 years and < 35 years, which is the standard for late birth.

4.4. Target sample size

The following will be set as the target number of patients for efficacy evaluation (the number of patients excluding miscarriages due to fetal chromosomal abnormalities).

Number of previous miscarriages: ≥ 6	: ≥ 10 per group	≥ 20 patients total
Number of previous miscarriages: 4, 5	: ≤ 30 /group	≤ 60 patients total
Total	: 40/group	Total 80 patients

[Rationale for setting]

As described below, patients with ≥ 4 previous miscarriages will be included in this study. According to the report on the rate of live births by the number of previous miscarriages by the research group on recurrent miscarriages, the rate was 34.2% in patients with 6 or more miscarriages, 58.8% in patients with 5 miscarriages, and 65% in patients with 4 miscarriages. By only enrolling patients with 4 or 5 previous miscarriages and setting strict inclusion and exclusion criteria, the proportion of patients with 4 previous miscarriages would be around 50% and the proportion of patients with 5 would be approximately 40%. Thus, the rate of live births in patients with 4 or more previous miscarriages in the placebo group in this study was estimated to be 40 to 50%. On the other hand, the live birth rate in patients with 6 or more previous miscarriages who received IVIG therapy obtained with the cooperation of the research group on recurrent miscarriages was 75%.

In this study, assuming that the live birth rate in the placebo group would be 42 to 48% and the live birth rate in the IVIG therapy group would be 75%, the sample size was calculated at $\alpha=0.05$ and $\beta=0.20$ and the results are shown in the table below. According to this table, if there are 40 patients in a group, the rate of live births in the placebo group would be 45%, which would secure power of 80% and, even if it is 48%, the power secured would be 70%. Thus, the number of patients in a group was set to be 40.

Table. Sample size and power to detect

Efficacy rate (live birth rate)		Power 80%		Power 70%	
Placebo group	IVIG group	Actual Power	N per Group	Actual Power	N per Group
0.42	0.75	0.803	34	0.702	27
0.43	0.75	0.801	36	0.708	29
0.44	0.75	0.809	39	0.710	31
0.45	0.75	0.803	41	0.710	33
0.46	0.75	0.805	44	0.708	35
0.47	0.75	0.805	47	0.702	37
0.48	0.75	0.802	50	0.706	40

4.5. Clinical study period

February 2014 to June 2021

5. Target population

5.1. Target disease

Target disease: Unexplained Recurrent Miscarriage

Among the patients whose risk factors for recurrent miscarriage are unknown who repeatedly miscarry or patients who repeatedly miscarry despite treatment for risk factors, those who meet the following inclusion criteria and do not meet any of the exclusion criteria are eligible for this study.

5.2. Inclusion Criteria

- (1) Patients with primary recurrent miscarriage
- (2) Patients with a history of at least 4 miscarriages (not including biochemical pregnancy in the count of prior miscarriages)
- (3) Patients with any of the following risk factors for recurrent miscarriage

- Patients with unknown risk factors

Patients with normal test results for each of the following risk factors who have experienced miscarriage of a fetus with normal chromosome karyotype

- 1) Abnormal uterine morphology*
- 2) Thyroid dysfunction
- 3) Chromosome abnormality in the couple
- 4) Positive antiphospholipid antibody**
- 5) Factor XII deficiency***
- 6) Protein S deficiency***
- 7) Protein C deficiency***

* An arcuate uterus will not be considered a risk factor.
** This refers to patients who meet the diagnostic criteria for antiphospholipid syndrome and patients with incidentally positive antiphospholipid antibody (see Appendix 6).
*** Determined by the investigator based on the results of measurement or the result of diagnosis, at the study site or another medical institution

- Patients determined to have risk factors

Patients with the following risk factors who have experienced miscarriage of a fetus with normal chromosome karyotype despite receiving treatment for these factors

- 1) Abnormal uterine morphology (septate uterus): Patients who have undergone surgery
 - 2) Thyroid dysfunction: Patients receiving medical treatment
 - 3) Incidentally positive antiphospholipid antibody (see Appendix 6; however, the latest test result should be negative), factor XII deficiency, protein S deficiency, protein C deficiency: Patients receiving combination therapy with aspirin and heparin
- (4) Regardless of whether or not risk factors are present, patients should have experienced at least 1 a miscarriage of a fetus with normal chromosome karyotype
 - (5) Patients below the age of 42 years at the time of obtaining informed consent

- (6) Patients who can be admitted for at least the period from the start date of administration of the study drug to the date of examination and assessment 1 week after the start of administration of the study drug
- (7) Patients who have given written informed consent to participate in this study

[Rationale for setting]

- (1) Patients who had never had a baby were enrolled to achieve a uniform patient background.
- (2) According to a report by the research group on recurrent miscarriages, the rate of ongoing pregnancy at 22 weeks of gestation significantly decreased with 6 or more prior miscarriages, and the conclusion was that "further improvement of treatment is necessary" ¹⁰⁾. In addition, even if the number of previous miscarriages is less than 6, miscarriages with normal fetal chromosomes repeatedly occur even with existing treatments such as heparin and aspirin, and there are patients for whom no other effective treatment methods are available. Thus, IVIG therapy is considered to have clinical significance if the efficacy is demonstrated in these patients. According to the report by the research group, the rate of ongoing pregnancy at 22 weeks of gestation is approximately 80% in patients with 3 or fewer miscarriages even with the conventional treatment; thus, the patients to be enrolled in this study were set to those with 4 or more previous miscarriages. Biochemical pregnancy was excluded since this is not included in the number of miscarriages according to the Japan Society of Obstetrics and Gynecology ⁴⁶⁾.
- (3) This was set as the definition of patients for whom the cause is unknown.
 - Patients with unknown risk factors
Since the research group on recurrent miscarriages is evaluating the 7 items described in this section as risk factors for recurrent miscarriage ¹⁰⁾, this study will also evaluate these 7 items and, if all are normal, the cause is considered to be unknown and thus was set in this manner. In addition, to exclude patients with accidental repeated miscarriages, this was set to those who miscarry infants with normal fetal chromosomes.
 - Patients with known risk factors
If a risk factor is known yet miscarriages recur regardless of treatment for the risk factor, the cause of recurrent miscarriage is considered unknown and thus was set in this manner. In addition, to determine treatment failure, this was set to those who miscarry infants with normal fetal chromosomes.
- (4) This criterion was set to exclude patients with accidental repeated miscarriages. According to the report by the research group, the rate of ongoing pregnancy at 22 weeks of gestation when the number of miscarriages was 4, 5, and 6 or more were 65.0%, 58.8%, and 34.2%, respectively, showing that relatively good results were obtained in patients with 4 or 5 previous miscarriages, suggesting that there were patients included who had not yet received adequate treatment. Patients had to have had at least one miscarriage of an infant with normal fetal chromosomes to select patients among these for whom no effective treatments were available and who would be candidates for IVIG therapy.
- (5) This criterion was set to prevent an increase in the number of patients excluded from the efficacy evaluation since the applicant plans to exclude miscarriages associated with fetal chromosomal abnormalities.
- (6) This criterion was set to ensure a system that allows close monitoring of subjective symptoms and objective findings and providing emergency treatment to patients receiving the investigational product.
- (7) This criterion was set in order to comply with the provisions concerning the protection of patients based on the "Guideline for Good Clinical Practice (GCP Ordinance)."

5.3. Exclusion Criteria

- (1) Patients with chromosome abnormalities in themselves or their partners that are risk factors for recurrent miscarriage, patients with antiphospholipid syndrome, and patients with incidentally positive antiphospholipid antibody (when the latest test result is positive)****
- (2) Patients in whom complications of diabetes mellitus or impaired glucose tolerance has been identified, but who have not received appropriate treatment for this condition
- (3) Patients who have received intravenous immunoglobulin therapy as treatment for recurrent miscarriage in the past
- (4) Patients with a history of stillbirth at 22 weeks of gestation or later
- (5) Patients receiving treatment for malignant tumor
- (6) Patients with a history of thromboembolism
- (7) Patients with a history of shock or hypersensitivity in response to the ingredients of this drug or patients with hereditary fructose intolerance
- (8) Patients who have been diagnosed with IgA deficiency in the past or patients who have a serum IgA level of <5 mg/dL at laboratory tests at registration
- (9) Patients who have received another study drug within the period of 12 weeks prior to informed consent or who are currently participating in another clinical trial
- (10) Patients who are unsuitable for this study for any other reason, in the opinion of a principal investigator or sub-investigators

**** See Appendix 6 for information on antiphospholipid syndrome and incidentally positive antiphospholipid antibody.

[Rationale for setting]

- (1) Chromosome abnormalities of couples were excluded since response to treatment with drugs was not expected. In addition, a decision was made to exclude IVIG therapy for antiphospholipid syndrome since IVIG therapy was effective not only in early pregnancy but also with multiple doses ^{47, 48)}, which was not consistent with the treatment plan for this study, and accidental positive antiphospholipid antibodies (however, a recent test must be positive) were also excluded since antiphospholipid syndrome was suspected.
- (2) This was adopted because "This should be controlled appropriately prior to attempting another pregnancy. Continued treatment after pregnancy is required" is stated in the "Recommendations on recurrent miscarriage management based on the research results of the Ministry of Health, Labour and Welfare Research Group" ⁴⁹⁾.
- (3) To closely evaluate the effect of the investigational product, patients were restricted to those who have not received IVIG therapy.
- (4) This intent is to evaluate the effect of IVIG in preventing miscarriages in this study; however, patients with a history of stillbirth from 22 weeks of gestation onwards may have delivered a child with conventional treatment. Thus, this criterion was set to homogenize the patients.
- (5) In general, patients receiving treatment for malignant tumors are likely to experience worsening of general condition, complications, and accompanying symptoms, etc.; thus, this criterion was set in consideration of safety and also because efficacy and safety evaluation may be difficult in some instances.
- (6) Cardiovascular or cerebrovascular disorders attributable to blood flow disorders associated with increased blood viscosity have been reported in patients treated with large doses of IVIG preparations; thus, this criterion was set in consideration of safety.
- (7) Since shock and anaphylaxis may occur (incidence: 0.1% to <5%), this criterion was set in

consideration of safety. In addition, as excipients, this drug contains D-sorbitol that is converted to fructose in the body, and then metabolized to fructose-1 phosphate (F-1-P). Patients with hereditary fructose intolerance are congenitally deficient in the enzyme that degrades F-1-P (aldolase B), and thus F-1-P may accumulate in the body, leading to hypoglycemia, etc., and thereby inducing hepatic failure and renal failure. Thus, these patients were excluded from the study.

- (8) Since patients with anti-IgA antibodies may develop hypersensitivity reactions when treated with this drug, this criterion was set in consideration of safety.
- (9) This criterion was set in consideration of safety and ethical considerations for patients.
- (10) This criterion was set so that whether or not to participate in this study can be judged in consideration of securing the safety of patients, taking into account general factors other than (1) to (9) above.

6. Obtaining informed consent from study participants and provision of information

6.1. Preparation of written information and informed consent form

The principal investigator will prepare the written information and informed consent form in cooperation with the sponsor. The written information and informed consent form will be considered a single document or a set of documents, and will be amended when necessary. The prepared and revised documents will be submitted to the sponsor and approved by the institutional review board (IRB) before the start of the study.

6.2. Information to be included in the informed consent form

- (1) That the study involves research
- (2) The study objectives
- (3) Name, job title, and contact information for the principal investigator
- (4) The study methods
- (5) Expected clinical benefits of the investigational product to the study participants' physical and mental health (if such benefits are not expected, to that effect) and anticipated disadvantages to study participants
- (6) Matters related to other treatment methods [availability and details of other therapies for the disease (important potential benefits and risks for such therapies)]
- (7) Duration of participation in the study (expected duration of participation)
- (8) Planned number participating in the study
- (9) That participation in the study is voluntary and that the study participant may withdraw from the study at any time
- (10) That the participant will not suffer any disadvantage by not taking part or withdrawing from the study
- (11) That monitors, auditors, IRBs, and regulatory authorities will have access to source documents (medical records), provided that participant confidentiality is maintained and in addition that, by signing or adding their name and seal to the informed consent form, the participant is authorizing such access
- (12) That the confidentiality of the participant will be maintained (even if the results are published)
- (13) That necessary treatments will be provided if any health injuries occur (that, if the participant experiences an adverse event that requires intervention, the participant will be notified)
- (14) The contact information for the study site in case of health injuries (the contact information for the study site to which the participant should send inquiries or should contact if they want further information on the study and their rights)

- (15) Matters concerning compensation for health injuries
- (16) That the participant will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the study
- (17) The foreseeable circumstances or reasons under which the participant's participation in the study may be terminated
- (18) Matters the participant must abide by
- (19) Information concerning the cost to be borne in association with the study (and the details of the cost to be borne by the participant, if any), and the details of any payments to the participant
- (20) That, if the participant has another primary care physician, the other primary care physician may be contacted provided consent is given
- (21) The type of IRB that reviews and evaluates the appropriateness of the study, etc., matters that each IRB reviews and evaluates, and other matters related to the IRB involved in the study
- (22) Other necessary matters related to the study

6.3. Timing and method of obtaining informed consent

The principal investigator (sub-investigator) will hand the informed consent form and other explanatory documents as needed to each patient who seem to meet the inclusion criteria and do not appear to meet any of the exclusion criteria, and give a full explanation of the contents before obtaining consent to participate in the study. After confirming that the patient has fully understood the contents, the principal investigator (sub-investigator) will obtain voluntary consent to participate in the study. If consent to participate in the study is obtained, the participant will sign/add their name and seal and date the informed consent form. The investigator (sub-investigator) who gave the explanation to the participant will also sign/add their name and seal and date the informed consent form. If a study collaborator gives a supplementary explanation, the study collaborator should also sign/add their name and seal, and date the form. A copy of the informed consent form will be given to the participant, and the original will be stored at the designated department in the study site or, if not specified, will be attached to the medical record. The date of informed consent will be recorded in the CRF.

6.4. Points to consider when obtaining consent

- (1) The principal investigator (sub-investigator) or study collaborator must not coerce or unfairly influence the participant to participate in the study or to continue participating in the study.

- (2) Verbal and written information provided at the time of informed consent must not contain any words that cause or suggest a waiver of a participant's rights or a release of the principal investigator (sub-investigator), study collaborator, study site, or sponsor from legal liability.
- (3) Explanations given at the time of informed consent should be written in language that is understandable to the participant and should be as non-technical as possible.

6.5. Preparation of participant screening list

The principal investigator will prepare a participant screening list, participant enrollment list, and participant identification list that include the participant identification codes and information that will be used for source document verification (e.g., date of informed consent) for all participants who provide informed consent.

6.6. Revision of written information and informed consent form

If information becomes available that may be relevant to the participant's willingness to continue participation in the study, the principal investigator (sub-investigator) must inform the subject immediately and confirm the participant's willingness to continue participation in the study.

In addition, if the principal investigator learns of any information that requires a revision to the informed consent form, the principal investigator will promptly revise the written information and informed consent form based on the information and submit it to the sponsor and for approval by the IRB.

If the written information and informed consent form are revised while the participant is participating in the study, the principal investigator (sub-investigator) will explain the revision of the written information and informed consent form each time, obtain the participant's consent to continue participation in the study, provide the participant with a copy of the revised informed consent form that is signed or has names and seals added and is dated, as well as the revised written information.

6.7. Contacting other primary physicians

The principal investigator (sub-investigator) will confirm whether or not the participant has other primary physicians they are visiting and, if the participant agrees, will inform the primary care physician about the participant's participation in the study. In addition, if the participant newly visits another primary physician during the study period, the participant will be instructed to contact the principal investigator (sub-investigator) and to show the wallet card or alternative document that is provided to indicate their participation in the study.

7. Investigational product

7.1. Name, etc. of investigational product

- (1) Investigational product code: GB-0998
- (2) Component: Human immunoglobulin G
- (3) Storage: Store at $\leq 10^{\circ}\text{C}$ and avoid freezing
- (4) Lot number: As printed on the investigational product label
- (5) Expiration date: As per the investigational product label

7.2. Dosage form and strength

The following two solution for injection formulations provided by the sponsor will be used in this study.

GB-0998: each vial (50 mL) contains 2,500 mg of normal human immunoglobulin G solution for injection

Placebo: each vial (50 mL) contains 450 mg of sodium chloride solution for injection (physiological saline)

7.3. Packaging and labeling

(1) Packaging form

Each vial of investigational product (GB-0998 or placebo) is placed in an individual package carton, and each carton is placed in an outer carton containing 10 individual package cartons.

(2) Labeling

The vial labels, individual packaging carton labels and outer carton labels are shown in Figures 7.1, 7.2, and 7.3.



Figure 7.1. Vial

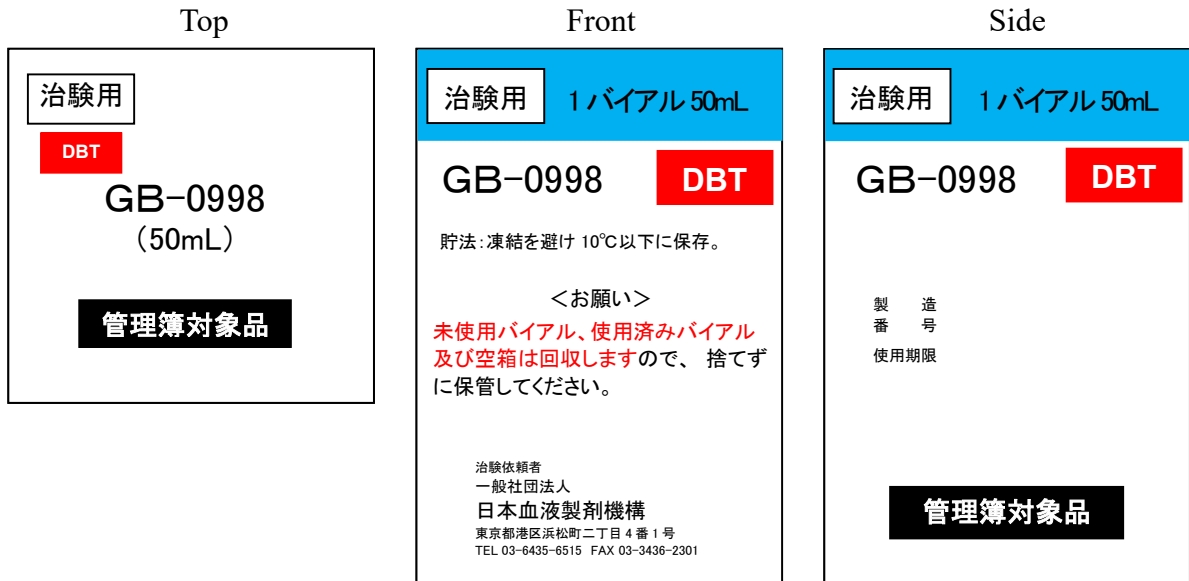


Figure 7.2. Individual package cartons

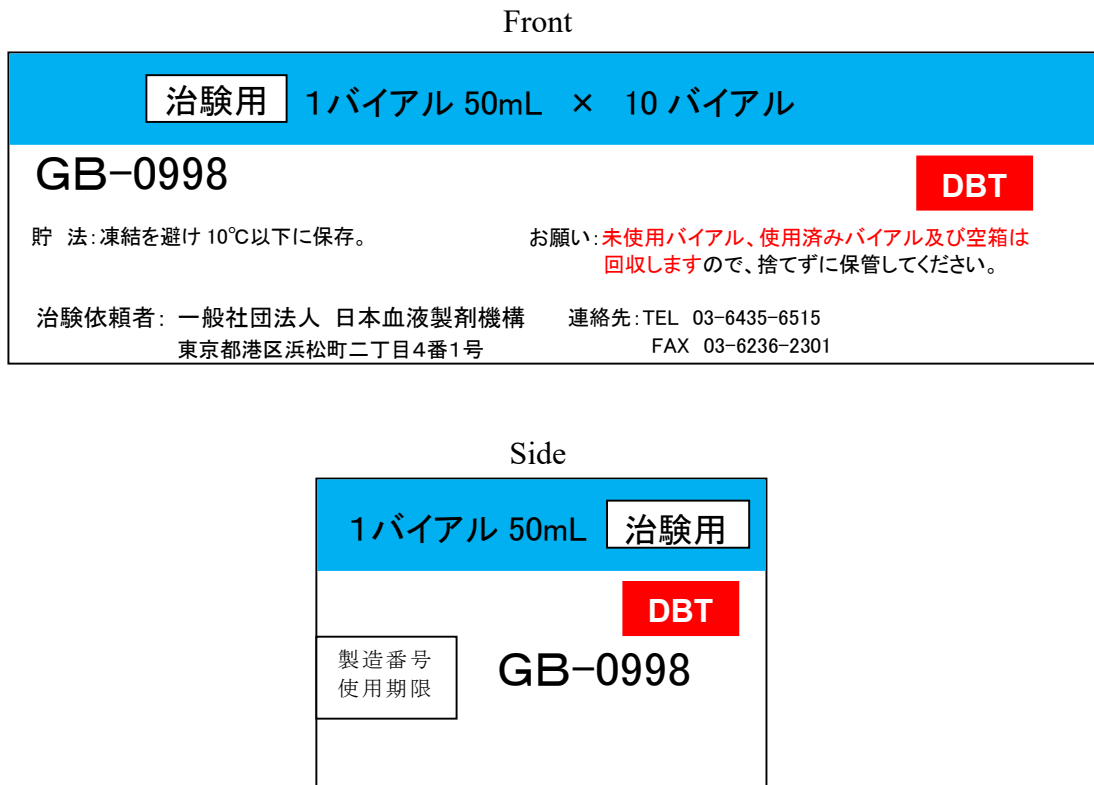


Figure 7.3. Outer carton

7.4. Investigational product management

(1) Delivery of investigational product

Sponsor will execute clinical study agreements with the study sites and issue investigational product to each study site after entering the study period specified in the agreement.

(2) Storage and management of investigational product

- 1) The investigational product manager and the individual in charge of investigational product management at the study site will appropriately store and manage investigational products in accordance with the procedures for investigational product management defined by the sponsor.
- 2) An investigational product management table will be prepared and records entered in order to gain an understanding of the status of use of investigational product and progress of the study, and a copy of the investigational product management table will be provided to the sponsor.
- 3) Similar to blood products (specified biological products), the investigational product in this study will be managed and logged in a blood product control log at each study site by using the seals attached to the investigational product, etc. and retained for the period specified in the PMD Act.

(3) Return of investigational product

- 1) The investigational product manager or the individual in charge of investigational product management at the study site will confirm the quantity of unused vials of investigational product and return the unused vials, used vials and empty cartons to the sponsor prior to breaking the key code. In doing so, the investigational product manager or the individual in charge of investigational product management will seal up the outer boxes and return these. Participant privacy and personal information privacy must be respected at the time of return.
- 2) If unused vials, used vials and empty cartons are discarded by mistake, the investigational product manager will report the reason in writing to the sponsor

(4) Preparation and retention of records

The investigational product manager or the individual in charge of investigational product management at the study site will record the receipt of investigational product shipments from the sponsor, inventory at the study site, usage by each participant, and return/destruction of unused and used vials and empty cartons to the sponsor and retain these records.

7.5. Confirmation of indistinguishability of investigational product

The appearance of the investigational product and the indistinguishability of the packaging are ensured by the investigational product randomization manager. The investigational product randomization manager will confirm the indistinguishability of the appearance and packaging of the investigational product at the time of randomization, at the end of use of investigational product due to lot changes, and prior to breaking the key code (at the end of the study).

8. Clinical study initiation procedures and schedule

- (1) The principal investigator (or sub-investigator) will confirm the eligibility of each patient in accordance with the following procedures and enroll the patient.

<Written informed consent>

- 1) Patients who qualify for the study and are found to be pregnant must provide written informed consent as described in Section 6.3.

<Eligibility confirmation and preparations prior to enrollment>

- 2) The principal investigator (sub-investigator) will assess participant demographics and IgA (unless the patient has a prior diagnosis of IgA deficiency) to confirm participant eligibility against the inclusion and exclusion criteria. In addition, body weight and ultrasound examinations of the gestational sac will be performed prior to enrollment. The IgA level will be measured at the study site or by the central laboratory; however, repeat measurements will not be required if historical data are available from other institutions.

<Enrollment>

- 3) The principal investigator (or sub-investigator) will fill out the enrollment form (Appendix 3) with the inclusion and exclusion criteria for each eligible patient, and contact the GB-0998 (recurrent miscarriage) registration center by fax by 5 weeks and 6 days of gestation.
- 4) The GB-0998 (recurrent miscarriage) registration center will confirm the eligibility of the reported patient and send the enrollment confirmation sheet (Appendix 4) to the principal investigator (or sub-investigator).
- 5) The principal investigator (or sub-investigator) will confirm that the patient has been enrolled using the enrollment confirmation sheet (Appendix 4) sent from the GB-0998 (recurrent miscarriage) registration center and confirm the assigned investigational product number.

The enrollment confirmation sheet should be archived appropriately.

<Testing, start of investigational product administration>

- 6) The principal investigator (or sub-investigator) will perform laboratory tests and start treatment with investigational product between 4 weeks and 0 days to 6 weeks and 6 days of gestation.

The number of weeks of gestation should be calculated based on obstetrically reasonable criteria, such as the last menstrual period, basal body temperature, and date of embryo transfer, and any of the calculation results being within the speci-

fied range is sufficient. The number of weeks of gestation and corresponding calculation criteria will be recorded in the CRF.

- 7) If modification of the registered information is required after enrollment, contact the GB-0998 (recurrent miscarriage) registration center.

GB-0998 (recurrent miscarriage) registration center

EPS Corporation

Acceptance period: April 2014 to September 2020

Fax no.: 0120-335728 (or 03-5225-6896)

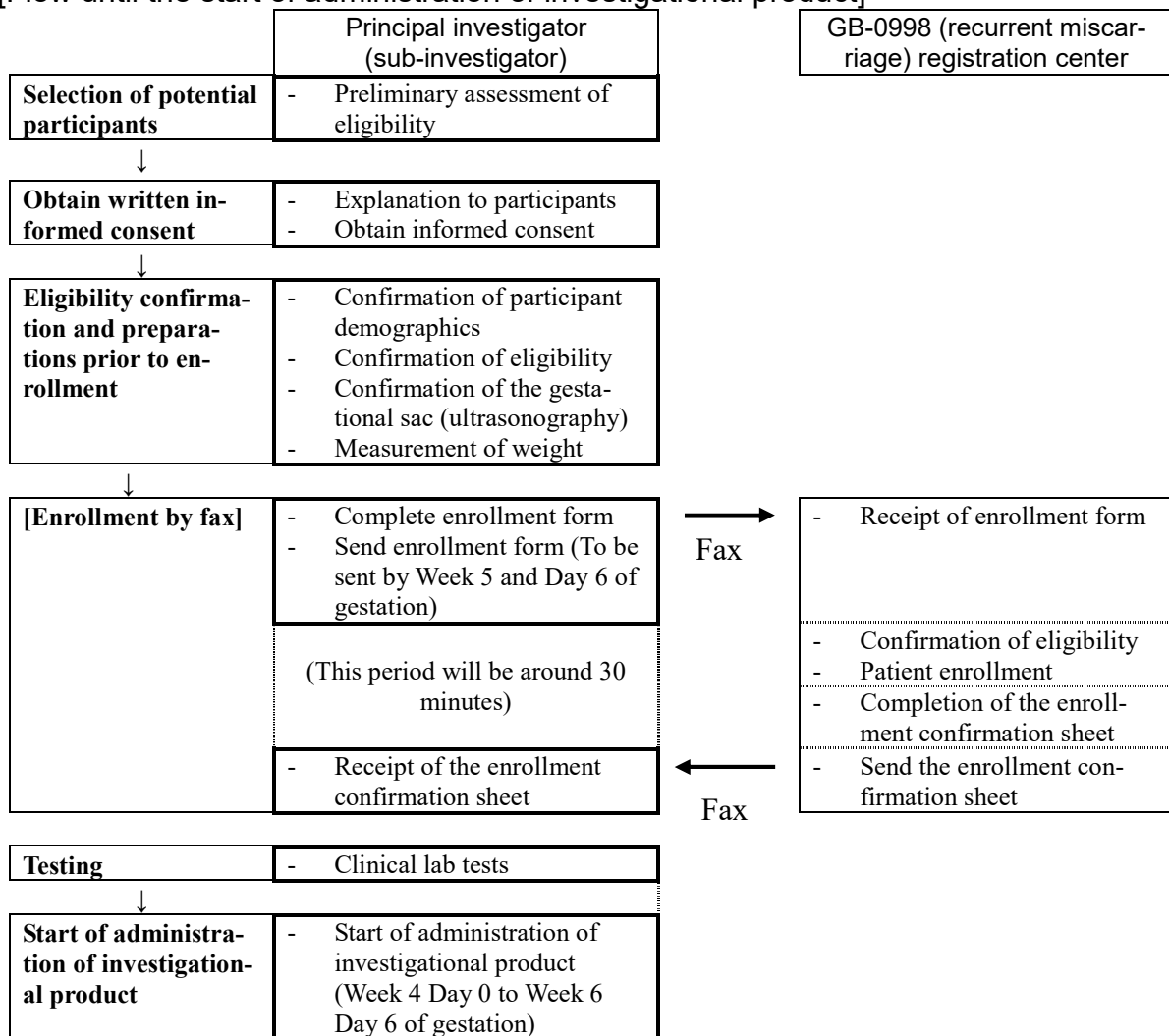
Tel. no.: 0120-077806 (or 03-5225-6845)

Open hours: Monday to Friday 9:00 to 18:00

(except Saturdays, Sundays, and national holidays and
12/29 to 1/4)

Faxes received after reception hours will be accepted during reception
hours the next open day

[Flow until the start of administration of investigational product]



(2) Study period

The study period will be from informed consent to discharge after childbirth or after miscarriage/stillbirth. If the patient is discontinued from the study, the procedures described in Section 16 will be followed. Adverse events occurring after the start of treatment with investigational product will be investigated.

9. Dosage and administration of investigational product

(1) Investigational product administration

Either GB-0998 or placebo will be administered once daily at a dose of 8 mL/kg body weight by intravenous infusion for 5 consecutive days. Administration of this product should be started after confirmation of the gestational sac by ultrasonography (from Week 4 Day 0 to Week 6 Day 6 of gestation). The number of weeks of gestation should be calculated based on obstetrically reasonable criteria, such as the last menstrual period, basal body temperature, and date of embryo transfer, and any of the calculation results being within the specified range is sufficient. The daily dose is the dose specified in the enrollment confirmation sheet (Appendix 4).

Venoglobulin® IH (VG-IH) will be administered at the infusion rate described in the package insert of VG-IH (excerpts shown below), with attention paid to the Precautions section. The start and stop times of administration will be recorded for each day of administration in the CRF.

Precautions concerning Dosage and Administration section of the package insert of VG-IH

Infusion rate: The initial infusion rate will be 0.01 mL/kg/min (0.6 mL/kg/hour) for 1 hour from the start of infusion on the first day and, if no abnormal findings such as adverse reactions are observed, the rate may be gradually increased. However, the rate should not exceed 0.06 mL/kg/min (3.6 mL/kg/hr). From Day 2 onwards, the infusion may be administered at the rate tolerated the previous day.

Precautions concerning Indications under the Precautions concerning Use section of the package insert of VG-IH

Preparation: 1) Avoid mixing the infusion with other drug products.
2) Do not use the residual solutions after use since bacterial contamination may occur (this product is a protein suitable for bacterial growth and does not contain preservatives).

At administration: 1) Administer the product after it returns to room temperature.
2) Do not use if the product is insoluble or cloudy
3) There is a potential for suspended particles to appear when this product is drawn up in syringes coated with silicone oil. Prior to administration, the drug solution should be inspected visually for suspended particles. Do not administer this product if suspended particles are observed.
4) Exercise caution to avoid extravascular leakage of the drug solution during intravenous administration. [In infants, extravascular leakage reportedly occurred during intravenous drip infusion, followed by skin ulcer and skin necrosis mainly at the infusion site.]

[Rationale for setting]

In Japan, IVIG therapy for autoimmune diseases such as Guillain-Barré syndrome (GBS), Chronic inflammatory demyelinating polyneuropathy (CIDP), and myasthenia gravis (MG) is approved at a dose of 400 mg (8 mL)/kg body weight/day x 5 consecutive days. Moreover, in terms of IVIG therapy for recurrent miscarriage, a Japanese clinical study reported that a favorable rate of live births was obtained with treatment at 20 g x 5 days of daily treatment, which is equivalent to 400 mg (8 mL)/kg body weight/day x 5 consecutive days of treatment. Based on the above, 400 mg (8 mL)/kg body weight/day x 5 consecutive days was selected as the dosage regimen for this study since the safety has been confirmed and treatment is generally accepted in patients with autoimmune diseases.

10. Concomitant medications

(1) Prohibited concomitant medications

The following medications are prohibited from the time of informed consent until miscarriage/stillbirth, delivery, or discontinuation.

- 5) Normal human immunoglobulin preparations other than the investigational product
- 6) Whole blood preparations
- 7) Fresh frozen human plasma
- 8) Other investigational products

[Rationale for setting]

- 1) This criterion was set because the investigational product is a product in the same class.
- 2) Since immunoglobulin G is contained in the plasma component and is considered to affect the efficacy evaluation, this was set accordingly.
- 3) Since immunoglobulin G is contained in the plasma component and is considered to affect the efficacy evaluation, this was set accordingly.
- 4) Since the evaluation has not been determined and there may be an effect on the efficacy and safety of the investigational product, this was set accordingly.

(2) Restricted concomitant medications

Administration of antithrombotic drugs such as aspirin and heparin and corticosteroids for treatment of recurrent miscarriage is allowed if the patient experienced a miscarriage of an infant with normal fetal chromosomes and treatment was confirmed to be ineffective, but the dose should not be increased until 22 weeks of gestation (however, this does not apply to minor dose adjustments for safety and dose modifications for low-dose aspirin therapy).

In addition, in patients with concomitant autoimmune diseases such as systemic lupus erythematosus (SLE), continuation of treatment is allowed if the patient has received corticosteroids for the treatment of autoimmune diseases and has had a subsequent miscarriage of an infant with normal fetal chromosomes.

[Rationale for setting]

If a miscarriage of an infant with normal fetal chromosomes occurs despite treatment with antithrombotic agents or corticosteroids, the treatment is considered ineffective; thus, continued treatment is allowed. In addition, patients who receive corticosteroids for the treatment of autoimmune diseases and experience a miscarriage of an infant with normal fetal chromosomes are allowed to continue treatment since this is not considered to affect the efficacy evaluation because the treatment is not considered to have prevented the miscarriage.

11. Blinding methods and maintenance of blinding

(1) Blinding methods

The study will be conducted in a double-blind manner. Blinding will be performed using GB-0998 and matching placebo.

Even after the completion of the study, all individuals involved in the study other than the investigational product randomization manager will remain blinded until the key code is broken. The appearance of investigational product and the indistinguishability of its packaging will be checked by the investigational product randomization manager at the time of randomization, at the end of use of investigational product due to lot changes, and prior to breaking the key codes (at the end of the study).

If an emergency key code is broken, the investigational product randomization manager will confirm, using the contents of the unblinding report, etc., that activities up to the unblinding had been performed in accordance with the specified procedures prior to unblinding.

(2) Maintenance of blinding

Investigational product blinding will be performed by pre-designated investigational product blinding personnel. After confirming the medication number described in the enrollment confirmation sheet (Appendix 4), the investigational product blinding personnel will cover the vial with an opaque blinding cover in order to keep the medication indistinguishable. Investigational product blinding personnel will not be involved in the administration of investigational product and the observation and evaluation of participants treated.

(3) Handling of laboratory data

Data on IgG, total protein, natural killer (NK) cell activity, and T regulatory cells (Tregs) after the start of treatment with investigational product will be stored in the central laboratory until the key code is broken, and will not be disclosed to each study site. After unblinding, the central laboratory will report the measurement results to the principal investigator at each study site and the sponsor.

In addition, after the start of investigational product therapy, IgG, total protein, NK cell activity, and Tregs will not be measured other than by the central laboratory until Week 16 Day 0 of gestation.

If an adverse event occurs that may involve changes in IgG, total protein, NK cell activity, or Tregs and the principal investigator determines that knowledge of this data is required to ensure participant safety, the principal investigator will notify the sponsor. The sponsor will contact the central laboratory using a predetermined method to report the relevant data of the patient to the principal investigators. The sponsor will document the

reason for the need to disclose the data and the extent to which the test results were shared.

12. Preparation and retention of key codes and emergency keys

After preparing the key code, the investigational product randomization manager will randomize investigational product according to the randomization procedure separately provided. The investigational product randomization manager will seal the key code immediately after randomization and keep it under strict control until the end of the study.

In addition, the investigational product randomization manager will also prepare the emergency key and keep it under strict control. The emergency key should not be broken except through a predetermined procedure. (Refer to Section "15.3. Procedure for breaking emergency keys during the study" for detailed procedures)

13. Procedure for breaking key codes

After all CRFs have been completed and the data collected in the CRFs have been locked, the investigational product randomization manager will break the key codes.

14. Surveillance and evaluation and timing of conduct

14.1. Participant demographics

The items shown in Table 14.1 will be investigated prior to the start of treatment with investigational product and entered into the CRF.

Table 14.1. Survey items related to participant demographics

Survey items
01) Date of birth
02) Body weight
03) Date used to calculate the number of weeks of gestation weeks (calculated from the last menstrual period, basal body temperature, or day of embryo transfer, etc.)
04) Complications
05) History of miscarriages [number of miscarriages, year and month of miscarriage and number of weeks of gestation per miscarriage, and results of chromosomal karyotype analyses (if testing is performed)]
06) Presence/absence and details of risk factors for recurrent miscarriage
07) Date of confirmation of gestational sac
08) Presence or absence, name, dose, timing of administration, and reason for administration of drugs used for treatment of recurrent miscarriage
09) Name and timing of previous therapies for the treatment of recurrent miscarriage

14.2. Efficacy

(1) Endpoints

Ultrasonography

(2) Timing of conduct

This will be performed prior to the start of administration of investigational product, 1 week after the start of administration of investigational product, at 8 weeks, 12 weeks, 16 weeks, 20 weeks, 22 weeks, 28 weeks, 32 weeks, and 36 weeks of gestation.

The acceptable windows for the timing of conduct are as follows.

- 1 week after the start of administration of investigational product: ± 1 day
- 8 to 20 weeks of gestation : ± 14 days
- 22 weeks of gestation : +14 days
- 28 to 36 weeks of gestation : ± 14 days
- At discontinuation : Date of discontinuation +14 days

(3) Primary endpoint

Ongoing pregnancy rate at 22 weeks of gestation (excluding miscarriages associated with fetal chromosomal abnormalities)

(4) Secondary endpoint

Ongoing pregnancy rate at 22 weeks of gestation (all patients)

Rate of live births (excluding miscarriages associated with fetal chromosomal abnormalities)

Rate of live births (all patients)

If the expected date of delivery is corrected prior to 22 weeks of gestation, the presence or absence of corrections, the corrected date, and corrected gestational week will be recorded in the CRF.

[Rationale for setting]

The Japan Society of Obstetrics and Gynecology defines miscarriage as delivery before 22 weeks of gestation ⁵⁰⁾, and beyond this period as a period when life can possibly be sustained outside the mother's body, although on the premise of receiving advanced neonatal treatment ⁵¹⁾. In this study, pregnancy continuing at 22 weeks of gestation is considered a response to this product, and the primary endpoint was set to the rate of Ongoing pregnancy at 22 weeks of gestation. Miscarriages due to fetal chromosomal abnormalities were excluded from the primary analysis since these occur incidentally regardless of the effect of the investigational product. In addition, the rate of live births was also selected as a secondary endpoint because it is an important index.

14.3. Safety

(1) Laboratory tests

1) Parameters

Hematology	Red blood cell (RBC) count, hemoglobin (Hb), hematocrit (Ht), white blood cell (WBC) count and WBC differentials [neutrophils (Neut), lymphocytes (Lym), monocytes (Mono), eosinophils (Eos), basophils (Baso)], platelet (Plt) count, D-dimer
Blood biochemistry	Total protein (TP), albumin (Alb), aspartate transaminase (AST/GOT), alanine transaminase (ALT/GPT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ -glutamyl transpeptidase (GTP), blood urea nitrogen (BUN), creatinine (CRE), uric acid (UA), sodium (Na), potassium (K), chloride (Cl), C-reactive protein (CRP)
Immunology	IgG, NK cell activity, Tregs
Urinalysis	Protein, glucose, urobilinogen

[Rationale for setting]

NK cell activity and Tregs were not measured as safety endpoints, but were measured for exploratory investigation since these are suggested to be related to the efficacy evaluation of IVIG therapy ^{52, 53)}. Other laboratory parameters were set as general parameters for safety evaluations.

2) Date of conduct

These will be performed prior to the start of and 1 week after the start of administration of investigational product, at 8 weeks, 16 weeks, and 22 weeks of gestation, at the time of miscarriage (not necessary if miscarriage occurs prior to the start of investigational product administration), or at the time of discontinuation prior to 22 weeks of gestation. Additionally, D-dimer will only be measured prior to the start of and 1 week after the start of investigational product treatment. NK cell activity and Tregs will be measured

only prior to the start of and 1 week after the start of investigational product treatment, and at 8 weeks of gestation. However, for D-dimer, the test will also be performed at the time of miscarriage if a miscarriage occurs after the start of investigational product administration and prior to the test 1 week after the start of administration and, for NK cell activity and Tregs, if a miscarriage occurs after the start of investigational product administration and prior to the test at 8 weeks of gestation.

The acceptable windows for the timing of conduct are as follows.

- Prior to starting of investigational product administration:
From enrollment to prior to starting investigational product administration
- 1 week after the start of administration of investigational product: ± 1 day
- 8 to 20 weeks of gestation : ± 14 days
- 22 weeks of gestation : +14 days
- At the time of miscarriage : +14 days
- At the time of discontinuation prior to 22 weeks of gestation:
Date of discontinuation +14 days

(2) Ultrasonography

1) Parameters

Fetal findings: crown-rump length, transverse diameter, femur length, presence/absence of abnormalities

2) Timing of conduct

This will be performed 1 week after the start of administration of investigational product, at 8 weeks, 12 weeks, 16 weeks, 20 weeks, 22 weeks, 28 weeks, 32 weeks, and 36 weeks of gestation and at discontinuation.

The acceptable windows for the timing of conduct are as follows.

- 1 week after the start of administration of investigational product : ± 1 day
- 8 to 20 weeks of gestation : ± 14 days
- 22 weeks of gestation : +14 days
- 28 to 36 weeks of gestation : ± 14 days
- At discontinuation : Date of discontinuation +14 days

[Rationale for setting]

Ultrasonography was set to confirm the timing of starting investigational product administration and the growth of fetuses.

(3) Observations during delivery or miscarriage/stillbirth

1) Items

Findings at birth: Number of weeks, method of delivery (vaginal delivery, cesarean section), presence/absence of maternal abnormalities

Findings in newborns: Infant weight, Apgar score (1 min, 5 min), presence/absence of abnormalities

Miscarriage/stillbirth findings: Number of weeks, karyotype analysis findings

2) Timing of conduct

Findings at the time of birth should be observed at the time of birth, findings at the time of miscarriage/stillbirth should be observed at the time of miscarriage/stillbirth (not required if the miscarriage occurs prior to the start of investigational product administration), and findings in newborns should be observed from the time of birth until discharge. However, the mother should be monitored for safety until discharge after delivery or discharge after miscarriage/stillbirth.

3) Other

If the participant is admitted to another medical institution due to an emergency birth, the responsible investigator will use the Medical Information Request Form to request the physicians at the inpatient medical institution to provide information on the participant and infant, and collect safety information, infant findings, etc. in writing.

(4) Adverse events

Definitions of adverse events are provided in Section 15.2. Any new or worsened subjective symptom or objective finding noted between the start of investigational product administration and discharge after childbirth or miscarriage/stillbirth is considered an adverse event. If abnormal laboratory values are to be regarded as adverse events, they should correspond to any of the following.

- 1) Changes in laboratory values that meet the definition of a serious adverse event
- 2) Changes in laboratory values that necessitate measures for investigational product treatment (dose reduction, interruption, and discontinuation).
- 3) Use of therapeutic drugs or treatments required due to changes in laboratory values
- 4) Surgical intervention needing to be performed due to changes in laboratory values
- 5) Does not meet the above criteria, but changes in laboratory values are medically notable as per the physician

If an adverse event occurs, appropriate measures should be taken as needed, and the contents shown in Table 14.2 should be entered in the CRF and reported to the sponsor. Refer to Table 14.3 for the criteria for severity of adverse events.

Table 14.2. Investigation of adverse events

[1] Adverse event term* ¹
[2] Type (whether it is a new onset or worsening of symptoms)
[3] Seriousness* ² (whether or not it is non-serious or serious)
[4] Severity* ³
[5] Date of onset
[6] Whether or not investigational product was discontinued
[7] Outcome and date of outcome
[8] Causal relationship to investigational product* ⁴ and reason for assessment
[9] Actions taken, medications
[10] Course of adverse event

*1: Adverse events are to be diagnoses. Events without diagnoses are signs, symptoms.

*2: Refer to Section 15.2. (3)

*3: Refer to Table 14.3

*4: Refer to Table 14.4

Table 14.3. Criteria for assessment of severity of adverse events

Severity	Criteria for assessment
1. Mild	Degree where actions* are not needed
2. Moderate	Degree where actions* are needed
3. Severe	Degree where particular emergency actions* are needed

*: Actions taken include administration of medication and performance of surgical procedures

The causal relationship to investigational product should be classified into 2 categories as shown in Table 14.4, taking into account the underlying disease, complications, concomitant medications, concomitant therapies, temporal relationship between the treatment and onset of adverse events, etc., and this information should be recorded in the CRF along with the reason for the classification. Moreover, once an adverse event occurs, it should be followed until resolution or until it has returned to the state prior to administration of investigational product. However, if further follow-up is deemed unnecessary and follow-up is terminated or if follow-up cannot be performed for any reason, the reason should be recorded in the CRF.

Table 14.4. Criteria for assessment of causal relationship to investigational product

Causal relationship	Criteria for assessment
1. Related	<p>There is at least a reasonable possibility that the investigational product is related to the adverse event. Reasonable possibility refers to the following items.</p> <ul style="list-style-type: none"> • Resolution observed after the discontinuation of investigational product • Recurrence observed after resumption of investigational product • Causality has already been established for the investigational product or similar products • No confounding risk factors • Consistent with exposure, duration • Accurate supporting medical history that almost certainly explains the involvement of investigational product • There is no reasonable possibility that the concomitant treatment is the cause
2. Not related	<p>There is no reasonable possibility that the investigational product is related to the adverse event.</p>

15. Ensuring the safety of study participants

15.1. Basic items

The principal investigator etc. must ensure that all participants are enrolled in accordance with the inclusion and exclusion criteria, and must determine eligibility based on laboratory tests, etc., to prevent enrollment of participants for whom safety cannot be ensured. During the course of the study, efforts will be made to ensure that the health of participants is monitored at all times through measures such as securing emergency contact methods for participants, and collecting and disseminating safety information that is considered related to the investigational product. Furthermore, if any adverse event occurs, the study should be discontinued or appropriate medical care provided to ensure participant safety.

15.2. Handling of onset of adverse events

(1) Definition of adverse events

An adverse event (AE) is any untoward medical occurrence during investigational product treatment. It does not necessarily have to have a causal relationship to the investigational product. That is, any unfavorable and unintended signs (including abnormal laboratory findings), symptoms, or diseases temporally associated with the use of investigational product, whether or not considered related to investigational product treatment. Refer to Section 14.3. (4) for the investigation of adverse events.

(2) Definition of adverse reactions

Among AEs, those judged to have a "related" causal relationship to investigational product are regarded as adverse reactions.

(3) Definition of serious adverse events

Among AEs, those corresponding to any of the following will be regarded as serious adverse events (SAEs).

- 1) Deaths
- 2) Those that result in death
- 3) Requires admission to a hospital or clinic or prolongation of hospitalization for treatment
- 4) Disability
- 5) Those that result in disability
- 6) Those that are serious in accordance with the above patients
- 7) Congenital disease or abnormalities in later generations

(4) Definition of expectedness (expected and unexpected)

The "expectedness" of an investigational product SAE is defined as follows.

Expected: Includes any event or synonym described in the IB or sent as a notification to participating study sites by the sponsor in writing and stored together with the IB.

Unexpected: The event is not "expected" as described above, or the nature or severity is not consistent with what is described in the IB.

(5) Actions to be taken at the onset of serious adverse events

In the event of an SAE, the principal investigator or sub-investigator will take appropriate measures and immediately notify the sponsor by telephone or facsimile* (using a standard form or site form), irrespective of the causal relationship to investigational product and the expectedness. In addition, the principal investigator will also prepare a detailed report (standard form or site form) including the causal relationship to investigational product and report this to the sponsor within 7 days.

The principal investigator will report the above SAEs to the head of their study site and the head of the study site will report the SAEs to the IRB.

In these instances, if the sponsor, the head of the study site, or the IRB asks for further information, the principal investigator will provide this.

*: Refer to **Appendix 1** for contact information.

(6) Reporting to regulatory authorities

If an SAE occurs and its causal relationship to the investigational product cannot be ruled out, the sponsor will report the event in an expedited manner to regulatory authorities in accordance with the criteria in **Table 15.1**, in accordance with Articles 80-2, Paragraph 6 and 80-4, Paragraph 3 of the PMD Act, Article 273 of the Enforcement Regulations of the PMD Act, "Reporting of Adverse Drug Reactions, etc. in Clinical Trials Involving Drugs" and Article 279 of the Enforcement Regulations of the PMD Act, "Reporting of Adverse Drug Reactions, etc. in Clinical Trials Involving Drugs or Devices to the PMDA." In addition to the aforementioned expedited reporting, periodic reports on the investigational product will be required to be submitted to the regulatory authorities for all SAEs listed in **Table 15.1** for which a causal relationship cannot be ruled out, including a list of all reported patients.

Table 15.1. Expedited reporting requirements and time frame

Expectedness	Seriousness	Reporting deadline
Unexpected	Death/Life-threatening	7 days
	Other serious events	15 days
Expected	Death/Life-threatening	15 days
	Other serious events	Reporting not required

15.3. Procedure for breaking emergency keys during the study

If an SAE is observed and the principal investigator believes it necessary to identify the investigational product to which the participant has been assigned to in order to ensure participant safety, the principal investigator will notify the sponsor. The sponsor will determine to break the emergency key for the participant using a predetermined method and notify the principal investigator of the result.

15.4. Expected adverse reactions

Clinically significant adverse reactions of GB-0998 include shock, anaphylaxis, hepatic function disorder, jaundice, meningitis aseptic, acute kidney injury, thrombocytopenia, pulmonary edema, thromboembolism and cardiac failure. Since similar adverse reactions may occur during the conduct of this study, careful attention will be paid to safety.

Refer to the IB for information on adverse reactions observed post-marketing and in other clinical studies.

16. Discontinuation criteria and procedures

16.1. Discontinuation criteria

If any of the following events occurs during the study period, the principal investigator (sub-investigator) will discontinue the relevant participant and take appropriate measures according to Section 16.2. Refer to Section 19 for criteria and procedures for terminating a study site or the overall study.

- (1) If the participant requests to be withdrawn from the study
- (2) If an AE occurs and continuation of the study is considered difficult
- (3) If the participant is found not meeting inclusion criteria or meeting exclusion criteria
- (4) If a deviation from the protocol is required for any medically unavoidable reason to eliminate an immediate hazard to the participant
- (5) If visits are missed
- (6) If the principal investigator (sub-investigator) judges it difficult to continue the study for any reason other than the above (1) to (5).

[Rationale for setting]

- (1) This criterion was set based on ethical consideration for participants.
- (2) This criterion was set in consideration of participant safety and ethical considerations.
- (3) This criterion was set since the participant would be ineligible for efficacy or safety evaluations.
- (4) This criterion was set in consideration of participant safety and ethical considerations.
- (5) This criterion was set since continuation of the study would not be feasible.
- (6) This criterion was set so that the appropriateness of continuation of the study can be judged if events important for safety other than (1) to (5) are observed.

16.2. Discontinuation procedures

- (1) If any of the discontinuation criteria is met, the principal investigator (sub-investigator) will explain this to the participant and withdraw the participant from the study. If necessary, appropriate measures should be taken. Surveys (laboratory tests, ultrasonography) will be conducted at the time of discontinuation, the presence or absence of AEs determined, and the date of discontinuation, reason for discontinuation, and other relevant information will be recorded in the CRF.
- (2) If any AE occurs, it should be followed up in principle until the symptoms disappear or the condition recovers to that prior to administration of investigational product.
- (3) If the participant is unable to complete assessments due to personal reasons (unable to make a visit, etc), the participant will be withdrawn from the study at that time. If the participant visits within 14 days of discontinuation, laboratory tests, ultrasound, and AE monitoring will be performed and CRFs completed. If a participant does not visit the study site within 14 days after discontinuation, the date of confirmation, method of contact (telephone, letter, etc.), reason for not visiting the study site, status (alive, lost to follow-up due to relocation, etc., death), and presence or absence of subsequent AEs

will be recorded based on details confirmed by the participant in the specified section for confirmation of the participant's health status in the CRF.

17. Statistical analysis

The details of the statistical analysis will be described in the statistical analysis plan to be separately prepared prior to locking patients.

17.1. Objectives of analyses

The objective is to demonstrate the efficacy of GB-0998 in the treatment of unexplained recurrent miscarriage based on the continuing rate of pregnancy at 22 weeks of gestation as the primary endpoint in comparison to placebo. In addition, the rate of live births will be compared as a secondary endpoint. The safety of GB-0998 will also be evaluated.

17.2. Analysis sets

The details of criteria for handling patients for analyses will be described in the statistical analysis plan. The sponsor will follow this standard and, in consultation with the medical expert as needed, will make patient handling decisions prior to databases lock.

(1) Intention-to-treat analysis set: ITT

The ITT will include all enrolled patients except those with a serious GCP violation (such as informed consent violations or contract violations), who do not have the target disease, with no administration of the investigational product or with no data for efficacy variables after the start of investigational product administration.

(2) Modified ITT analysis set: Modified-ITT

The Modified-ITT is the ITT population excluding miscarriages due to fetal chromosome abnormalities.

(3) Per Protocol Set: PPS

The PPS will include all patients in the Modified-ITT except those with a serious protocol violation (such as inclusion criteria violations, exclusion criteria violations, significant administration/dosage violations, significant concomitant medications violations or allocation violations).

(4) Safety Analysis Set

The safety analysis set will include all enrolled patients except those with a serious GCP violation (such as informed consent violations or contract violations), with no administration of the investigational product or with no data for safety variables after the start of the investigational product administration.

(5) The primary efficacy analysis set will be the Modified-ITT. The same analyses as those for the Modified-ITT will be performed for the ITT and PPS, which will also be described in the statistical analysis plan.

17.3. Statistical analysis methods

(1) Participant demographics

Each item will be tabulated by treatment group, and the demographic characteristics of participants will be evaluated. Frequency distribution tables will be prepared for categorical data and summary statistics (mean, standard deviation, median, etc.) will be calculated for continuous data. Between-group bias will be tested using Fisher's exact tests or chi-squared tests, and continuous data will be tested using t-tests or Wilcoxon tests.

(2) Efficacy evaluations: primary endpoint

The ongoing pregnancy rate at 22 weeks of gestation (excluding patients with miscarriages due to fetal chromosomal abnormality) will be calculated with its 95% confidence interval. The comparison between groups will be tested using Fisher's exact tests and Mantel-Haenszel chi-squared tests adjusted for number of prior miscarriages.

(3) Efficacy evaluations: secondary endpoints

Evaluations of ongoing pregnancy rate at 22 weeks of gestation (all patients) and live birth rate (excluding patients with miscarriages due to fetal chromosomal abnormality, all patients) will be performed in the same manner as for the primary endpoint.

(4) Safety evaluations

The incidence of adverse events and adverse reactions will be determined and compared by treatment group. In addition, the incidence and number of individual adverse events and adverse reactions will be determined by treatment group. A listing of adverse events will also be provided. Changes in laboratory test values will be shown for each patient.

17.4. Level of significance and confidence intervals

The level of significance will be two-sided 5% and the confidence interval will be 95%.

18. Protocol adherence, deviations or changes, and amendments

18.1. Adherence to the clinical study protocol

To attest that the principal investigator and the sponsor agree on the contents of and compliance with the protocol, the principal investigator will sign or add their name and seal and date the protocol agreement (Appendix 5). The same applies when the protocol is amended.

18.2. Deviations from or changes of the protocol

- (1) The principal investigator (sub-investigator) will document all deviations from the protocol that occur. The principal investigator will only prepare a document describing the details of and reasons for deviations that do not comply with the protocol for medically unavoidable reasons, such as to avoid an immediate hazard to participants, immediately submit this to the sponsor and the head of the study site, and retain a copy of the document.
- (2) The principal investigator (sub-investigator) may deviate from or change the protocol for medically unavoidable reasons, such as to eliminate an immediate hazard to study participants, without prior written agreement from the sponsor or prior approval from the IRB. In this instance, the principal investigator will submit the details of and reasons for the deviation or change and, if an amendment to the protocol is appropriate, submit a draft to the sponsor, the head of the study site, and the IRB via the head of the study site as soon as possible to obtain approval, and also obtain agreement from the sponsor via the head of the study site using the clinical study protocol agreement (Appendix 5).
- (3) The principal investigator will promptly submit a report to the sponsor, the head of the study site and the IRB via the head of the study site, on any change to the study that significantly affects the conduct of the study or increases the risk to participants.

18.3. Amendments of the protocol

- (1) If the sponsor learns about matters related to the quality, efficacy, and safety of the investigational product or other information that is important for the proper conduct of the study, the sponsor will revise the study protocol as needed.
- (2) If a protocol is amended, the sponsor will fully discuss the amendment and the conduct of the study in accordance with the amendment with the principal investigator, and obtain an agreement with the principal investigator using the clinical study protocol agreement (Appendix 5). The amended protocol will also be submitted to the head of the study site and the IRB via the head of the study site. The same procedure will be

followed if a protocol is amended at the direction of the IRB or the head of the study site.

However, this does not apply to changes related only to administrative aspects of the study (for example, a monitor or a phone number change).

- (3) This protocol will not be revised in association with the revision of Appendices. The sponsor will submit the revised appendices to the principal investigator as needed.

19. Completion or discontinuation and interruption of the study

19.1. Study completion

The principal investigator will submit the study completion report to the head of the study site promptly after study completion.

The head of the study site will notify the IRB and the sponsor of this report (completion of the study and summary of results) in writing.

19.2. Study discontinuation or interruption

(1) Procedures for discontinuation or interruption of the overall study

- 1) In the event of discontinuation or interruption of the overall study, the sponsor will promptly notify the heads of all study sites involved in the study and the regulatory authorities in writing of this and the detailed reasons.
- 2) If notified of a decision to discontinue or interrupt the overall study by the sponsor, the head of the study site will promptly send notification of the decision and the reason in writing to the principal investigators and the IRB.
- 3) Upon receipt of notification of discontinuation or interruption of the overall study, the principal investigator will promptly inform participants participating in the study of this, provide appropriate medical care, and take other necessary measures.

(2) Procedures for discontinuation or interruption of the study at individual study sites

- 1) If the study is discontinued or interrupted, the principal investigator will promptly notify the head of the study site of the discontinuation or interruption and the reason in writing and explain the details of the discontinuation or interruption.
- 2) If the principal investigator reports the discontinuation or interruption of the study, the head of the study site will promptly send notification to the sponsor and the IRB and explain the details of the discontinuation or interruption in writing.

20. Case report forms

20.1. Format of case report forms to be used in the study

Double-blind, parallel-group comparative study of GB-0998 in patients with recurrent miscarriage of unknown cause

- Case report form [1] [Demographics/Medications]
- Case report form [2] [Follow-up]
- Case report form [3] [Pregnancy outcomes/Completion, discontinuation]
- Case report form [4] [Adverse events]

20.2. Precautions during completion and modifications or changes

(1) Completion of case report forms

- 1) The principal investigator (sub-investigator) will complete CRFs for each participant receiving investigational product. The study collaborator may fill out the contents that do not require medical judgment, such as transcriptions from medical records.
- 2) Entries will be completed with black or blue ballpoint pen or ink.
- 3) Applicable items in multiple choice entry fields will be circled or checked.
- 4) The form will be completed with the appropriate information or data.
- 5) If a required field is left blank, the reasons (not performed, not applicable, etc.) or a slash will be entered to distinguish these from missing entries.

(2) Corrections or changes to case report forms

Corrections and changes to CRFs will be made according to the guidance provided by the sponsor.

1) Prior to submission to the sponsor

Any correction or change should not obscure the original entry. That is, when a correction or change is made directly to the CRF, the original entry should be crossed out with a double line so that it can be read, and the correction or change should be signed or a seal affixed, and dated, and the reason for the correction or change should be provided, if necessary. Correction fluid should not be used. For major or significant corrections or changes, the reason should be provided.

2) After submission to the sponsor

A dedicated correction or modification form specified by the sponsor will be used.

(3) Submission of case report forms

- 1) The principal investigator (sub-investigator) or study collaborator will complete the CRFs accurately according to the protocol.
- 2) The sub-investigator or the study collaborator who was involved in completion of the CRF will sign or add their name and seal to the designated space. The princi-

pal investigator must sign or add their name and seal to the space provided and add the date on which the contents of the CRF were checked.

- 3) The principal investigator will promptly submit the CRFs to the sponsor after completion of the study for each participant. In addition, a copy of the records will be retained.
- 4) The principal investigator must ensure that the CRFs submitted to the sponsor are accurate, complete, legible, and submitted in a timely manner and that participant identification codes are used to identify study participants.
- 5) Data reported in the CRFs that are based on source documents must be consistent with the source documents. If there are any discrepancies, the principal investigator will prepare records explaining the reasons, submit this to the sponsor, and retain a copy.

20.3. Identification of contents in case report forms that should be regarded as source data

Data in the CRFs will be considered source data for the following, unless otherwise documented in the source documents.

- (1) Presence or absence of complications before pregnancy
- (2) Presence or absence of drugs used for the treatment of recurrent miscarriage before enrollment and reasons for use
- (3) Presence or absence of therapies used for the treatment of recurrent miscarriage before enrollment
- (4) Whether or not laboratory tests (central measurement) and ultrasonography were performed, presence or absence of abnormalities
- (5) Presence/absence and reason for use of concomitant medications since enrollment, and presence/absence and reason for use of concomitant therapies since enrollment
- (6) Category, type, seriousness, severity, outcome, date of outcome, causal relationship to investigational product, and reason for assessment of adverse events
- (7) Study completion/discontinuation, reason for discontinuation
- (8) Principal investigator's (sub-investigator's) comments

If any content other than the above is adopted, this will be specified in a separate document between the sponsor and the principal investigator before the start of the study.

21. Direct access to source documents

(1) Direct access

The head of the study site and the principal investigator will cooperate with monitoring and auditing activities conducted by the sponsor, and inspections by the IRB and regulatory authorities, and provide direct access to all study-related records, including source documents, upon request.

(2) Method of direct access

The sponsor will directly access records in accordance with their own GCP standard operating procedures. However, the identification of source documents at each study site, and the method, timing, and items to be inspected by the sponsor will be performed after separate consultation with relevant parties.

For source data that are recorded in more than one source document, physician records (medical records) will be identified as the preferred source for direct access.

22. Quality control and quality assurance of the study

The study site and the sponsor will perform data quality control and quality assurance activities in accordance with study-related standard operating procedures and mutually agreed upon documents, and the sponsor's GCP audit standard operating procedures.

22.1. Quality control

- (1) The investigator (sub-investigator) will complete the CRFs in accordance with the protocol.
- (2) In the event of a protocol deviation, the principal investigator (sub-investigator) will record all deviations for whatever reason. The principal investigator will only prepare a document describing the details of and reasons for deviations that do not comply with the protocol for medically unavoidable reasons, such as to avoid an immediate hazard to participants, immediately submit this to the sponsor and the head of the study site, and retain a copy of the document.
- (3) Data reported in the CRFs that are based on source documents must be consistent with the source documents. If there are any discrepancies, the principal investigator will prepare records explaining the reasons, submit this to the sponsor, and retain a copy.
- (4) The principal investigator will certify that the data in the CRFs, etc. to be submitted to the sponsor are accurate and complete based on the records, etc. described in (1) to (3) above.
- (5) The monitor will conduct monitoring based on agreement with the study site to ensure that the human rights, safety, and wellbeing of study participants are protected, that the study is conducted in compliance with the latest protocol and GCP, and that study data, etc. reported by the principal investigator (sub-investigator) are accurate, complete, and verifiable from source documents and other study-related records.
- (6) The principal investigator and the head of the study site will provide the monitor with necessary information including access to source documents such as medical records.
- (7) The individual in charge of data management will prepare a data management plan in accordance with operating procedures, perform quality control at each stage of data handling, and ensure quality.
- (8) All laboratory tests other than for IgA will be tested centrally by the central laboratory in order to standardize the assay methods for laboratory tests.

22.2. Quality assurance

- (1) The sponsor will establish an auditing department that is independent from the clinical study department and will conduct audits at an appropriate time to ensure the quality of the study.

- (2) The principal investigator and the head of the study site will provide necessary information, including access to medical records and other source documents, if requested by the sponsor's auditor, IRB, or regulatory authorities.

23. Ethical conduct of the study

23.1. Institutional review board

(1) Review of the conduct of the study

Prior to the start of the study, the IRB will review the protocol, case report form (sample), and informed consent form, and evaluate the acceptability of the study from an ethical and scientific perspective, after which the study will be conducted after approval is obtained.

(2) Review of continuation, etc. of the study

1) Review of continuation of the study

The principal investigator will submit a written summary of the current status of the study to the head of the study site once a year or more frequently at the request of the IRB. The head of the study site will then request the IRB to review the appropriateness of continuing the study.

2) Other reviews

The head of the study site will request a review by the IRB on continuing participation in the study if notification from the sponsor of a serious and unexpected adverse reaction is received, if notification of a serious adverse event is obtained from the principal investigator, if information that is considered to affect the willingness of the participant (and their legal representative) to continue participation in the study is obtained and notification from the principal investigator is obtained that the informed consent form has been revised, or otherwise considered necessary by the head of the study site.

23.2. Matters concerning the protection of human rights of study participants

(1) This study will be conducted with the highest respect for the spirit of the Declaration of Helsinki.

(2) The principal investigator (or sub-investigator) will select participants as described below.

1) From an ethical and scientific perspective, the participant's health condition, symptoms, age, ability to give consent, dependence on the principal investigator (sub-investigator), participation in other clinical studies, etc. will be carefully considered in accordance with the objectives of the study.

2) Participants who lack the capacity to provide consent will not be selected.

- 3) Careful consideration will be given to participants who may be unfairly disadvantaged by not participating in the study, so that their consent may be given voluntarily.
- (3) Records that may identify the participant will be safeguarded in consideration of protecting the participant's privacy and confidentiality.

24. Records retention

24.1. Records to be retained at the study site

The individual responsible for records retention specified by the head of the study site will archive essential documents to be archived at the study site until the later of either of the following (1) or (2). If the sponsor considers a longer period of retention necessary, the study site will discuss the retention period and method with the sponsor.

In addition, if the sponsor decides not to include the clinical results data collected in the present study to the application for marketing approval, the sponsor will notify the head of the study site of this decision and the reason in writing.

- (1) The day on which marketing approval of the investigational product is obtained (or the day 3 years after the date of discontinuation of development or the date of receipt of notification that the results of the clinical study will not be included in the application for approval, if applicable)
- (2) The day 3 years after the date of discontinuation of the overall study or completion of the clinical study

In addition, if marketing approval for the investigational product has been obtained or the sponsor has decided to discontinue development without obtaining marketing approval, the sponsor will report this in writing to the head of the study site.

24.2. Records to be retained by the sponsor

The sponsor will retain essential documents to be retained by the sponsor until either of the following (1) or (2), whichever comes later.

- (1) The day 5 years after the date of marketing approval of the investigational product (or the day 3 years after the date of the decision to discontinue development, if applicable) or the day of completion of reexamination
- (2) The day 3 years after the date of discontinuation of the overall study or completion of the clinical study

25. Monetary payments

The costs associated with this study will be paid to each study site by the sponsor according to the agreement with each study site. If payments are to be made to participants, these will be through the study site in accordance with the rules of each study site after discussion over the method of payment, etc.

If the study site outsources the management, etc. of expenses associated with the clinical study to a third party, the payee, method of payment, etc. will be separately discussed and an agreement reached.

26. Compensation for health injuries and insurance

26.1. Compensation for health injuries

If a participant suffers from a health injury due to the conduct of this study, appropriate compensation will be paid according to the standard defined by the sponsor [Compensation covers medical expenses (out-of-pocket costs), medical allowances, and benefits]. In this instance, the participant will not be burdened with proof of causality, etc.

However, health injuries that correspond to any of the following (1) to (6) shall be excluded from the scope of compensation.

- (1) If the causal relationship to the study is ruled out
- (2) If the injury is clearly attributable to other incidental factors
- (3) If the adverse event is due to intentional actions or gross negligence at the study site
- (4) If it is due to intentional actions of the participant
- (5) If it is clear that the adverse event was caused intentionally or due to the negligence of a third party
- (6) If there was a failure to provide therapeutic benefit, including the expected effects of the investigational product, to participants (in the event of a health injury associated with the worsening of the underlying disease)

In addition, in the following instances in (7) to (9), the amount of compensation may be reduced, or all or part of the compensation may not be paid.

- (7) If the participant's health injury is reasonably attributable to other factors
- (8) If the health injury occurred to the participant due to their gross negligence
- (9) If the cause of the participant's health injury was due to the site's negligence

26.2. Insurance

The sponsor will take necessary measures such as obtaining insurance in order to ensure the fulfillment of liability for compensation and indemnification of study-related health injuries that occur to participants.

27. Agreement regarding publications

The information contained in this protocol is the sole property of the sponsor and will be provided to the personnel involved in the study such as the principal investigator (sub-investigator) who will conduct this clinical study and the IRB, but must not be disclosed to third parties without written agreement from the sponsor except when necessary for the conduct of the study.

In addition, if information obtained from the study is to be disclosed to outside parties, such as at an academic meeting, by study site personnel involved in the study such as the principal investigator (sub-investigator), a written request for publication must be sent in advance to the sponsor and written approval obtained from the sponsor.

The sponsor may freely use the information obtained in this study for the purpose of reporting to the regulatory authorities, proper use of the drug, marketing, etc. and, in such instances, due attention will be paid to the protection of participants' privacy.

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