

Review Report

August 10, 2016

Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency.

Brand Name	Kenketu Glovenin-I for I.V. Injection 500 mg, Kenketu Glovenin-I for I.V. Injection 2500 mg, Kenketu Glovenin-I for I.V. Injection 5000 mg
Non-proprietary Name	Freeze-dried Polyethylene Glycol-treated Human Normal Immunoglobulin
Applicant	Nihon Pharmaceutical Co., Ltd.
Date of Application	November 5, 2015
Dosage Form/Strength	Lyophilized powder for solution for injection: Each vial contains 500, 2500, or 5000 mg of Polyethylene Glycol-treated Human Normal Immunoglobulin G.
Application Classification	Prescription drug, (4) Drug with a new indication
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug III

Results of Review

Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded, as per the attachment, that the efficacy of the product in the treatment of patients with Guillain-Barré syndrome (GBS) (patients with severe GBS in the acute exacerbation phase and difficulty in walking) has been demonstrated, and its safety is acceptable in view of its observed benefits.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below.

Indications

1. Agammaglobulinemia or hypogammaglobulinemia
2. Coadministration with antibiotics for the treatment of severe infection
3. Idiopathic thrombocytopenic purpura (ITP) (for patients with ITP unresponsive to other drugs who have a marked bleeding tendency and who require temporary hemostasis during emergency procedures including surgery and delivery)
4. Kawasaki's disease (KD) in the acute phase (for patients with severe KD who have a risk of coronary artery disorder)
5. Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy)
6. Pemphigus (for patients with pemphigus inadequately responsive to corticosteroids)
7. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (for patients with SJS or TEN inadequately responsive to corticosteroids)

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA will not be responsible for any consequence resulting from the use of this English version.

8. Bullous pemphigoid (BP) (for patients with BP inadequately responsive to corticosteroids)¹⁾
9. Guillain-Barré syndrome (GBS) (for patients with severe GBS in the acute exacerbation phase and difficulty in walking)
(Underline denotes additions.)

Dosage and Administration

Kenketu Glovenin-I should be reconstituted with the supplied solvent (Water for Injection [the Japanese Pharmacopoeia]) to a concentration of 500 mg/10 mL. The reconstituted solution should be administered according to the regimens specified below for each indication. Direct intravenous injection should be given at a very slow rate.

Agammaglobulinemia or hypogammaglobulinemia:

The usual dosage of human immunoglobulin G is 200 to 600 mg (in 4-12 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection once every 3 to 4 weeks. The dose may be adjusted according to the patient's condition.

Coadministration with antibiotics for the treatment of severe infection:

The usual dosage of human immunoglobulin G is 2500 to 5000 mg (in 50-100 mL) for adults, and 100 to 150 mg (in 2-3 mL)/kg body weight for children, administered by an intravenous infusion or a direct intravenous injection. The dose may be adjusted according to the patient's condition.

Idiopathic thrombocytopenic purpura:

The usual daily dosage of human immunoglobulin G is 200 to 400 mg (in 4-8 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection. If symptoms do not improve after 5-day intravenous immunoglobulin treatment, the treatment should be discontinued. The dose may be adjusted according to the patient's age and condition.

Kawasaki's disease in the acute phase:

The usual dosage of human immunoglobulin G is 200 mg (in 4 mL)/kg body weight administered once daily for 5 days by an intravenous infusion or a direct intravenous injection, or 2000 mg (in 40 mL)/kg body weight administered by a single intravenous infusion. The dose for 5-day administration may be decreased or increased according to the patient's age and condition, and the dose for single-dose administration may be decreased according to the patient's age and condition.

Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy)

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion or a direct intravenous injection. The dose may be decreased according to the patient's age and condition.

Pemphigus:

¹⁾ The application for partial change to add an indication for "bullous pemphigoid (if corticosteroids are not sufficiently effective)" was approved on November 20, 2015 after submitting the present application.

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion. The dose may be decreased according to the patient's age and condition.

Stevens-Johnson syndrome and toxic epidermal necrolysis:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

Bullous pemphigoid¹⁾:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

Guillain-Barré syndrome:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

(Underline denotes additions.)

Review Report (1)

June 14, 2016

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

Product Submitted for Approval

Brand Name	Kenketu Glovenin-I for I.V. Injection 500 mg, Kenketu Glovenin-I for I.V. Injection 2500 mg, Kenketu Glovenin-I for I.V. Injection 5000 mg
Non-proprietary Name	Freeze-dried Polyethylene Glycol-treated Human Normal Immunoglobulin
Applicant	Nihon Pharmaceutical Co., Ltd.
Date of Application	November 5, 2015
Dosage Form/Strength	Lyophilized powder for solution for injection: Each vial contains 500, 2500, or 5000 mg of Polyethylene Glycol-treated Human Normal Immunoglobulin G.
Proposed Indication	<ol style="list-style-type: none"> 1. Agammaglobulinemia or hypogammaglobulinemia 2. Coadministration with antibiotics for the treatment of severe infection 3. Idiopathic thrombocytopenic purpura (ITP) (for patients with ITP unresponsive to other drugs who have marked bleeding tendency and who require temporary hemostasis during emergency procedures including surgery and delivery) 4. Kawasaki's disease (KD) in the acute phase (for patients with severe KD who have a risk of coronary artery disorder) 5. Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy) 6. Pemphigus (for patients with pemphigus inadequately responsive to corticosteroids) 7. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (for patients with SJS or TEN inadequately responsive to corticosteroids) 8. <u>Guillain-Barré syndrome (GBS) (for patients with severe GBS in the acute exacerbation phase and difficulty in walking)</u> <p>(Underline denotes additions.)</p>

Proposed Dosage and Administration

Kenketu Glovenin-I should be reconstituted with the supplied solvent (Water for Injection [the Japanese Pharmacopoeia]) to a concentration of 500 mg/10 mL. The reconstituted solution should be administered according to the regimens specified below for each indication. Direct intravenous injection should be given at a very slow rate.

Agammaglobulinemia or hypogammaglobulinemia:

The usual dosage of human immunoglobulin G is 200 to 600 mg (in 4-12 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection once every 3 to 4 weeks. The dose may be adjusted according to the patient's condition.

Coadministration with antibiotics for the treatment of severe infection:

The usual dosage) of human immunoglobulin G is 2500 to 5000 mg (in 50-100 mL) for adults, and 100 to 150 mg (in 2-3 mL)/kg body weight for children, administered by an intravenous infusion or a direct intravenous injection. The dose may be adjusted according to the patient's condition.

Idiopathic thrombocytopenic purpura:

The usual daily dosage of human immunoglobulin G is 200 to 400 mg (in 4-8 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection. If symptoms do not improve after 5-day intravenous immunoglobulin treatment, the treatment should be discontinued. The dose may be adjusted according to the patient's age and condition.

Kawasaki's disease in the acute phase:

The usual dosage of human immunoglobulin G is 200 mg (in 4 mL)/kg body weight administered once daily for 5 days by an intravenous infusion or a direct intravenous injection, or 2000 mg (in 40 mL)/kg body weight administered by a single intravenous infusion. The dose for 5-day administration may be decreased or increased according to the patient's age and condition, and the dose for single-dose administration may be decreased according to the patient's age and condition.

Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy)

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion or a direct intravenous injection. The dose may be decreased according to the patient's age and condition.

Pemphigus:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion. The dose may be decreased according to the patient's age and condition.

Stevens-Johnson syndrome and toxic epidermal necrolysis:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

Guillain-Barré syndrome:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

(Underline denotes additions.)

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List of Abbreviations

ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
FAS	Full Analysis Set
FG	Functional Grade
γ -GTP	Gamma-glutamyltransferase
GBS	Guillain-Barré Syndrome
IAPP	Immunoabsorption Plasmapheresis
IVIG	Intravenous Immunoglobulin
Kenketu Glovenin-I	Kenketu Glovenin-I for I.V. Injection 500 mg, Kenketu Glovenin-I for I.V. Injection 2500 mg, and Kenketu Glovenin-I for I.V. Injection 5000 mg
MedDRA	Medical Dictionary for Regulatory Activities
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
PA	Plasma Absorption
PE	Plasma Exchange
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Plasma Perfusion
PT	Preferred Term
SJS	Stevens-Johnson Syndrome
SMQ	Standardised MedDRA Queries
SOC	System Organ Class

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Kenketu Glovenin-I for I.V. Injection (“Kenketu Glovenin-I”) is lyophilized powder for solution for injection containing freeze-dried polyethylene glycol-treated human normal immunoglobulin G as the active ingredient. Kenketu Glovenin-I was approved in Japan in October 1984 for the indications of “agammaglobulinemia or hypogammaglobulinemia” and “coadministration with antibiotics for the treatment of severe infection.” After that, the product was approved for the following indications: “idiopathic thrombocytopenic purpura (for patients with ITP unresponsive to other drugs who have marked bleeding tendency and who require temporary hemostasis during emergency procedures including surgery and delivery)” in January 1986, “Kawasaki’s disease in the acute phase (for patients with severe KD who have a risk of coronary artery disorder)” in July 1993, “improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy)” in June 1999, “pemphigus (for patients with pemphigus inadequately responsive to corticosteroids)” in October 2008, “Stevens-Johnson syndrome and toxic epidermal necrolysis (for patients with SJS or TEN inadequately responsive to corticosteroids)” in July 2014, and “bullous pemphigoid (for patients with BP inadequately responsive to corticosteroids)” in November 2015. The last one was approved after submission of the present application.

As of October 2015, Kenketu Glovenin-I has not been approved outside Japan.

In Japan, Freeze-dried Sulfonated Human Normal Immunoglobulin (brand name, Kenketsu Venilon-I) is available as a drug product indicated for the treatment of “Guillain-Barré syndrome (GBS) (for patients with severe GBS in the acute exacerbation phase and difficulty in walking).”

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

Since the current application is intended for addition of a new indication, no new “data relating to quality” were submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although the current application is intended for addition of a new indication, no new “non-clinical pharmacology data” were submitted because the freeze-dried sulfonated human normal immunoglobulin preparation, a product with the same pharmacological activity as freeze-dried polyethylene glycol-treated human normal immunoglobulin, is approved for the indication of “Guillain-Barré syndrome (for patients with severe GBS in the acute exacerbation phase and difficulty in walking) and has successfully undergone the re-examination.

4. Non-clinical Pharmacokinetic and Outline of the Review Conducted by PMDA

Since the current application is intended for addition of a new indication, no new “non-clinical pharmacokinetic study data” were submitted.

5. Toxicology and Outline of the Review Conducted by PMDA

Since the current application is intended for addition of a new indication, no new “toxicology data” were submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

Since the current application is intended for addition of a new indication, no new “biopharmaceutic studies and clinical pharmacology data” were submitted.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results of a Japanese phase III study in Japanese patients with GBS (5.3.5.2-1, Study NPB-01-13/C-01) as the efficacy and safety evaluation data. Also, the applicant submitted Japanese and foreign published literature, guidelines, textbooks, etc., as the efficacy and safety reference data.

7.1 Japanese phase III study (5.3.5.2-1, Study NPB-01-13/C-01 [■ 2014 to ■ 2015])

An open-label, uncontrolled study was conducted to investigate the efficacy and safety of Kenketu Glovenin-I in patients who had a confirmed diagnosis of GBS based on the diagnostic criteria (CTD

5.4-15), adapted from the criteria of Asbury et al. (CTD 5.4-1), and who were assessed as severe²⁾ by the Hughes functional grading scale (FG),³⁾ and the patients had GBS in the acute exacerbation phase⁴⁾ (target sample size, 21 patients).

Kenketu Glovenin-I (400 mg/kg/day) was administered by intravenous infusion for 5 days with a 12-week follow-up period.

A total of 22 patients were treated with Kenketu Glovenin-I and all the patients treated were included in the safety analysis. Of the 22 patients, 20 were included in the full analysis set (FAS) for efficacy analysis, and the remaining 2 were excluded from the analysis because they were found to have diseases other than GBS. Three patients discontinued the study due to the use of prohibited concomitant drugs/therapies (2 patients) or change of hospital (1 patient).

The primary endpoint of the study was the proportion of patients with improvement by ≥ 1 grade in Hughes FG score from baseline at 4 weeks.⁵⁾ The proportion of such patients [95% confidence interval (CI)] was 65.0% [40.8%, 84.6%] (13 of 20 patients) with the lower limit of the 95% CI exceeding the pre-set threshold (39%).

Adverse events (including laboratory abnormalities) were noted in 22 of 22 patients (100%). No death occurred. Serious adverse events were noted in 2 patients (calculus urinary and chronic inflammatory demyelinating polyradiculoneuropathy [CIDP] in 1 patient each), but their causal relationship to the study drug was ruled out.

Adverse events (including laboratory abnormalities) for which a causal relationship to the study drug could not be ruled out were noted in 16 of 22 patients (72.7%). Major events were headache (8 patients), hepatic enzyme increased (4 patients), alanine aminotransferase (ALT) increased (4 patients), aspartate aminotransferase (AST) increased (3 patients), pyrexia (2 patients), drug eruption (2 patients), and white blood cell count decreased (2 patients).

Vital signs (blood pressure, pulse rate, and body temperature) did not show any clinically significant changes.

According to the applicant, these results suggested the efficacy of Kenketu Glovenin-I in GBS patients without any significant safety concern.

7.2 Japanese and foreign published literature, guidelines, textbooks, etc.

Intravenous immunoglobulin (IVIG) therapy is recommended for the treatment of GBS. The recommended dosage regimen is 400 mg (in 8 mL)/kg/day administered by intravenous infusion for 5 days.

Submitted reference materials

CTD 5.4-9: *Lancet*. 2005;366:1653-1666

CTD 5.4-15: Guidelines for the treatment of Guillain-Barré syndrome (GBS)/chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), https://www.jsnt.gr.jp/guideline/img/meneki_4.pdf

CTD 5.4-16: *Practical Guideline for Guillain-Barré Syndrome and Fisher Syndrome 2013*. Nankodo; 2013

CTD 5.4-23: *BMJ*. 2008;337:227-231

CTD 5.4-44: *Handbook of Neurology*. 4th ed. Igaku-Shoin; 2010:1027-1030

²⁾ Patients with predominant motor neuropathy who were assessed as grade 4 or 5 in Hughes FG score (grade 3 patients are included if their symptoms are progressive)

³⁾ 0, healthy; 1, minor symptoms or signs of neuropathy but capable of running; 2, able to walk ≥ 5 m without a walker, stick, or support, but unable to run; 3, able to walk ≥ 5 m with a walker, stick, or support; 4, confined bed- or wheel chair-bound; 5, requiring assisted ventilation; 6, death

⁴⁾ Patients able to start treatment with the study drug within 2 weeks (up to 4 weeks) after onset

⁵⁾ Subjects discontinuing the study within 4 weeks after the start of treatment were to be classified as non-improved, but no subjects fell under this category.

- CTD 5.4-45: *Textbook of Neurology for Medical Students and Residents*. 2nd revised ed. Chugai-igakusha; 2014:276-278
- CTD 5.4-46: *Merritt's Neurology*. 13th ed. Lippincott Williams & Wilkins; 2016:760-771
- CTD 5.4-47: *Netter's Neurology*. 2nd ed. Saunders; 2011:672-681
- CTD 5.4-48: *Adams & Victor's Principles of Neurology* 10th ed. McGraw-Hill Medical; 2014;1322-1330
- CTD 5.4-49: *Eur J Neurol*. 2008;15:893-908

7.3 Clinical reports, etc.

The applicant submitted 16 foreign published reports and 11 Japanese published reports on IVIG therapy for GBS. In this section, data from 11 randomized, controlled studies and 1 report of the use-results survey of freeze-dried sulfonated human normal immunoglobulin are described.

7.3.1 Neurology. 1996;46:100-103 (CTD 5.4-3)

An open-label, randomized, parallel group comparative study was conducted to investigate the efficacy and safety of IVIG therapy and plasma exchange (PE) therapy in non-Japanese GBS patients aged ≥ 14 years who had a confirmed diagnosis based on the criteria of Asbury et al. and had a Hughes FG score of ≥ 2 .

In the IVIG therapy group, immunoglobulin (0.5 g/kg/day) was administered by intravenous infusion once daily for 4 days, and in the PE therapy group, a total volume of 200 to 250 mL/kg of plasma was exchanged in 5 sessions over 7 to 10 days.

Of 50 randomized subjects (26 in the IVIG therapy group, 24 in the PE therapy group), 44 subjects (26 in the IVIG therapy group, 18 in the PE therapy group) were included in the efficacy analysis, and the remaining 6 subjects in the PE therapy group were excluded from the analysis (1 subject whose diagnosis was changed to CIDP and 5 subjects with protocol violation).

The proportion of subjects with improvement by ≥ 1 grade in Hughes FG score at 1 month after treatment (the primary efficacy endpoint) was 69% in the IVIG therapy group and 61% in the PE therapy group. The median time to improvement by 1 grade in Hughes FG score was 14.0 days in the IVIG therapy group and 16.5 days in the PE therapy group.

Complications were experienced by 5 subjects in the IVIG therapy group and 19 subjects in the PE therapy group. Major complications were hypotension, arrhythmia, pneumonia, inappropriate antidiuretic hormone secretion syndrome, deep vein thrombosis/pulmonary embolism, sepsis, localized phlebitis, and urinary tract infection. No death occurred.

7.3.2 Eur Neurol. 2001;46:107-109 (CTD 5.4-4)

An open-label, randomized, parallel group, comparative study was conducted to investigate the efficacy and safety of IVIG, PE, and immunoabsorption plasmapheresis (IAPP) therapies in non-Japanese patients with moderate to severe GBS within the first 14 days after symptom onset (target sample size, 279 patients).

Subjects in the IVIG therapy group received immunoglobulin (0.4 g/kg/day) intravenously once daily for 5 days, subjects in the PE therapy group received 5 sessions of PE therapy, and subjects in the IAPP therapy group received 5 sessions of IAPP therapy.

Of 76 randomized subjects⁶⁾ (25 in the IVIG therapy group, 26 in the PE therapy group, 25 in the IAPP therapy group), 67 subjects who received the allocated treatment (23 in the IVIG therapy group, 26 in the PE therapy group, 18 in the IAPP therapy group) were included in the safety analysis. Of the 67 subjects treated, 55 subjects (20 in the IVIG therapy group, 21 in the PE therapy group, 14 in the IAPP therapy group) were included in the efficacy analysis.

⁶⁾ A report favoring IVIG therapy over other therapies was published, which affected the enrollment of patients, resulting in the discontinuation of enrollment after 76 subjects were registered.

The proportion of subjects with improvement by ≥ 1 grade in functional score at 28 days after randomization (the primary endpoint) was 80.0% (16 of 20 subjects) in the IVIG therapy group, 71.4% (15 of 21 subjects) in the PE therapy group, and 50.0% (7 of 14 subjects) in the IAPP therapy group.

Adverse events were noted in 12 of 23 subjects (52.2%) in the IVIG therapy group, 14 of 26 subjects (53.8%) in the PE therapy group, and 11 of 18 subjects (61.1%) in the IAPP group. Serious adverse events related to the treatment were noted in 1 subject in the IVIG therapy group (arrhythmia absoluta/tachycardia/chills/pyrexia/shortness of breath) and 1 subject in the PE therapy group (hepatic rupture/splenic rupture/death).

7.3.3 Medical Consultation & New Remedies. 2013;50:1103-1128 (CTD 5.4-11)

A use-results survey was conducted to investigate the safety and efficacy of freeze-dried sulfonated human normal immunoglobulin in Japanese patients with GBS.

The safety analysis population consisted of 1184 subjects (1335 episodes) and the efficacy analysis was performed on 1097 episodes. Freeze-dried sulfonated human normal immunoglobulin was administered to 180 patients at < 400 mg/kg/day, to 904 patients at 400 to 800 mg/kg/day, and to 2 patients at ≥ 800 mg/kg/day. The treatment duration was ≥ 5 days in most cases.

The primary efficacy endpoints were the proportion of episodes⁷⁾ with improvement by ≥ 1 grade in FG score (Hughes FG or FG for infants⁸⁾) score at 4 weeks after the start of treatment with freeze-dried sulfonated human normal immunoglobulin⁹⁾ treatment, or days required to achieve improvement by 1 grade in FG score (median time estimated by Kaplan-Meier curve). As a result, the proportion of episodes with improvement by ≥ 1 grade in FG score was 69.4% (761 of 1097 episodes) after the first dose and 53.8% (84 of 156 episodes) after the second dose. The time required to achieve improvement by 1 grade in FG score was 12 days after the first dose and ≥ 28 days after the second dose.

Adverse drug reactions occurred in 380 of 1184 patients (32.1%). The incidence of adverse drug reactions among observed episodes was 30.5% (356 of 1169 episodes) after the first dose and 24.7% (41 of 166 episodes) after the second dose. Major adverse drug reactions included ALT increased (90 events), AST increased (90 events), hepatic function abnormal (89 events), white blood cell count decreased (35 events), headache (32 events), neutrophil count decreased (27 events), platelet count decreased (22 events), eosinophil count increased (20 events), liver disorder (18 events), rash (18 events), pyrexia (18 events), dyshidrosis (17 events), meningitis aseptic (16 events), nausea (15 events), and monocyte count increased (10 events). Serious adverse drug reactions occurred in 41 of 1184 patients (3.5%). Major adverse drug reactions included meningitis aseptic (6 events), hepatic function abnormal (6 events), white blood cell count decreased (5 events), and neutrophil count decreased (5 events).

7.3.4 N Engl J Med. 1992;326:1123-1129 (CTD 5.4-14)

An open-label, randomized, parallel group, comparative study was conducted to investigate the efficacy and safety of IVIG and PE therapies in non-Japanese patients aged ≥ 4 years who had a confirmed diagnosis of GBS based on the criteria of Asbury et al., showed a functional score of ≥ 3 ,¹⁰⁾ and were unable to walk 10 m independently (target sample size, 200 patients [100 per group]). Treatment was started within the first 2 weeks after symptom onset.

In the IVIG therapy group, immunoglobulin (0.4 g/kg/day) was administered intravenously once daily for 5 days, and in the PE therapy group, a total volume of 200 to 250 mL/kg of plasma was exchanged in 5 sessions over 7 to 14 days.

⁷⁾ Patients with unknown FG or with missing FG data were excluded from analysis.

⁸⁾ 0, healthy; 1, minor symptoms or signs of neuropathy and gross movement of upper and lower limbs possible; 2, able to stand (able to sit in patients unable to stand before disease onset) without support for a short time period; 3, gross movement of lower limbs possible but unable to stand (or sit) without support; 4, gross movement of lower limbs impossible and lying supine in bed; 5, requiring assisted ventilation; 6, death

⁹⁾ In patients discharged within 4 weeks, the FG score at discharge was used. In patients whose FG was evaluated more than once at approximately 4 weeks post-dose, the FG score on the day closest to Week 4 was used.

¹⁰⁾ 0, healthy; 1, minor symptoms or signs of neuropathy and capable of physical work; 2, able to walk ≥ 10 m without support; 3, able to walk ≥ 10 m with a walker or support; 4, confined bed- or chair-bound (unable to walk ≥ 10 m even with a walker or support); 5, requiring assisted ventilation (at least partially during the day); 6, death

Of 150 randomized patients, 147 patients (74 in the IVIG therapy group, 73 in the PE therapy group) were included in the safety and efficacy analyses, and the remaining 3 patients were excluded from the analyses (2 patients with other disease and 1 patient with unstable angina¹¹⁾).

The proportion of subjects with improvement by ≥ 1 grade in functional score at 4 weeks after the treatment (the primary endpoint) was 53% in the IVIG therapy group and 34% in the PE therapy group (between-group comparison, $P = 0.024$, χ^2 test). The median time required to achieve improvement by 1 grade in functional score was 27 days in the IVIG therapy group and 41 days in the PE therapy group (between-group comparison, $P = 0.05$, log-rank test).

Treatment-related adverse events were noted in 5 subjects in the IVIG therapy group, which were blood pressure decreased (2 subjects), dyspnoea, body temperature increased, and microscopic haematuria (1 subject each). At 2 weeks after treatment, ALT increased¹²⁾ was noted in 63% of subjects in the IVIG therapy group and 42% of subjects in the PE therapy group, with a subsequent decrease in the parameter. No subjects were diagnosed with chronic liver disorder. One death occurred in the IVIG therapy group (cardiovascular complications) and 2 deaths in the PE therapy group (cardiovascular complications and untreatable airway spasm in 1 subject each).

7.3.5 Neurological Therapeutics. 2001;18:69-81 (CTD 5.4-17)

An open-label, randomized, parallel group, comparative study was conducted to investigate the efficacy and safety of IVIG therapy and PE therapy¹³⁾ in Japanese patients aged ≥ 16 and < 65 years who had a confirmed diagnosis of GBS based on the criteria of Asbury et al. and had a Hughes FG score of 4 or 5 (patients with a score of 3 were included if their symptoms were progressive). As a general rule, treatment was started within the first 2 weeks (up to 4 weeks) after symptom onset.

In the IVIG therapy group, immunoglobulin (400 mg/kg/day) was administered intravenously once daily for 5 days, and in the PE therapy group, a total volume of 200 to 250 mL/kg of plasma was exchanged in up to 7 sessions over 4 weeks.

Of 53 randomized subjects (27 in the IVIG therapy group, 26 in the PE therapy group), 47 subjects (23 in the IVIG therapy group, 24 in the PE therapy group) were included in the safety and efficacy analyses, and 4 subjects in the IVIG group (who did not receive the study drug) and 2 subjects in the PE therapy group (who were diagnosed with non-target disease after the start of treatment) were excluded from the analyses.

The proportion of subjects with improvement by ≥ 1 grade in Hughes FG score at 4 weeks after treatment, (the efficacy endpoint) was 60.9% (14 of 23 subjects) in the IVIG therapy group and 65.0% (13 of 20 subjects) in the PE therapy group (between-group comparison, $P = 0.780$, χ^2 test). The time required to achieve improvement by 1 grade in Hughes FG score (50% value estimated by Kaplan-Meier curve) was 14 days in the IVIG therapy group and 20 days in the PE therapy group (between-group comparison, $P = 0.853$, generalized Wilcoxon test).

Adverse events (excluding laboratory abnormalities) were noted in 5 of 23 subjects (21.7%) in the IVIG therapy group and 7 of 24 subjects (29.2%) in the PE therapy group, which were all mild or moderate in severity. Laboratory abnormalities were noted in 10 of 23 subjects (43.5%) in the IVIG therapy group and 4 of 24 subjects (16.7%) in the PE therapy group. All the adverse events were mild or moderate in severity. One death occurred in the PE therapy group, but its causal relationship to the study drug was ruled out.

7.3.6 Lancet. 1997;349:225-230 (CTD 5.4-19)

An open-label, randomized, parallel group, comparative study was conducted to investigate the efficacy and safety of IVIG therapy, PE therapy, and combination of PE and IVIG therapies (PE + IVIG therapy)

¹¹⁾ The patient with unstable angina was excluded from the study because PE therapy is contraindicated in patients with unstable angina.

¹²⁾ ALT increased was defined as ≥ 1.5 -fold increase in ALT from the upper limit of the reference range.

¹³⁾ Either IAPP therapy, membrane separation, or centrifugal separation was used.

in non-Japanese patients with GBS aged ≥ 16 years who had a confirmed diagnosis of GBS based on the criteria of Guillain-Barré Syndrome Study Group (CTD 5.4-7) and were unable to walk independently (target sample size, 366 patients [122 per group]). Treatment was started within the first 14 days after symptom onset.

In the IVIG therapy group, immunoglobulin (0.4 g/kg/day) was administered intravenously once daily for 5 days. In the PE therapy group, a total volume of 250 mL/kg of plasma was exchanged in 5 to 6 sessions over 8 to 13 days. In the PE + IVIG therapy group, a total volume of 250 mL/kg of plasma was exchanged in 5 sessions, and starting on the day following the completion of plasma exchange, immunoglobulin (0.4 g/kg/day) was administered intravenously once daily for 5 days.

Of 383 randomized subjects (122 in the IVIG therapy group, 132 in the PE therapy group, 129 in the PE + IVIG therapy group), 379 subjects (121 in the IVIG therapy group, 130 in the PE therapy group, 128 in the PE + IVIG therapy group) were included in the safety and efficacy analyses, and the remaining subjects were excluded from the analyses (1 subject in the IVIG therapy group [misdiagnosis], 2 subjects in the PE therapy group [misdiagnosis and treatment initiated at >14 days after symptom onset in 1 subject each], and 1 subject in the PE + IVIG therapy group [treatment initiated at >14 days after symptom onset]).

The primary efficacy endpoint of the study was the change in severity score¹⁴⁾ at 4 weeks after randomization. The mean change in severity score and its standard deviation was -0.8 ± 1.3 in the IVIG therapy group, -0.9 ± 1.3 in the PE therapy group, and -1.1 ± 1.4 in the PE + IVIG therapy group. The proportion of subjects unable to walk independently at 48 weeks was 16.7% (19 of 121 subjects) in the IVIG therapy group, 16.5% (21 of 130 subjects) in the PE therapy group, and 13.7% (17 of 128 subjects) in the PE + IVIG therapy group.

Adverse drug reactions were noted in 6 subjects in the IVIG therapy group and in 8 subjects in the PE therapy group. In the PE + IVIG therapy group, PE therapy-related adverse drug reactions were noted in 6 subjects, and IVIG therapy-related adverse drug reactions in 9 subjects. Major adverse drug reactions were nausea and vomiting (2 subjects each) in the IVIG therapy group and hypotension in the PE therapy group (5 subjects). Among adverse reactions reported in the PE + IVIG therapy group, hypotension (3 subjects) was associated with PE therapy, and chills (4 subjects) and pyrexia (2 subjects) were associated with IVIG therapy. Six deaths occurred in the IVIG therapy group, 5 in the PE therapy group, and 8 in the PE + IVIG therapy group.

7.3.7 Crit Care. 2011;15;R164 (CTD 5.4-25)

A randomized, parallel group, comparative study was conducted to investigate the efficacy and safety of IVIG and PE therapies in non-Japanese pediatric patients who had a confirmed diagnosis of GBS based on the criteria of van Doorn et al. (*Lancet Neurol.* 2008;7:939-950) and were judged to require mechanical ventilation according to the pre-defined criteria. Treatment was started within the first 14 days after the occurrence of muscle weakness.

In the IVIG therapy group, immunoglobulin (0.4 g/kg/day) was administered intravenously once daily for 5 days, and in the PE therapy group, plasma exchange was performed for 5 days.

A total of 41 randomized subjects (20 in the IVIG therapy group, 21 in the PE therapy group) were included in the safety and efficacy analyses.

The primary endpoint of the study was the duration of ventilator use. The median duration of ventilator use and its standard deviation was 13.0 ± 2.1 days in the IVIG therapy group and 11.0 ± 1.5 days in the PE therapy group (between-group comparison, $P = 0.037$, Mann-Whitney test).

No serious adverse drug reaction was reported.

¹⁴⁾ 0, healthy without signs or symptoms of GBS; 1, minor symptoms or signs of neuropathy and capable of running; 2, able to walk 5 m without support; 3, able to walk 5 m with a walker, stick, or support; 4, bed- or chair-bound, unable to walk as in 3; 5, requiring assisted ventilation (at least during some time of the day); 6, death

7.3.8 *Pediatrics. 2005;116:8-14 (CTD 5.4-26)*

A randomized, parallel group, no-treatment-controlled study was conducted to investigate the efficacy and safety of IVIG therapy in non-Japanese pediatric patients aged ≤ 18 years who had a confirmed diagnosis of GBS based on the criteria of Asbury et al. and were able to walk independently (Study 1 in patients able to walk 5 m independently). Separately, a randomized, parallel group study was conducted to compare the efficacy and safety of IVIG therapy between different dosage regimens (Study 2 in patients unable to walk 5 m independently¹⁵).

In Study 1, immunoglobulin (1 g/kg/day) was administered intravenously for 2 days. In Study 2, immunoglobulin 1 g/kg/day was administered intravenously once daily for 2 days or immunoglobulin 0.4 g/kg/day was administered intravenously for 5 days.

In Study 1, a total of 21 subjects were randomized (14 in the IVIG therapy group, 7 in the no-treatment group), and all the subjects were included in the efficacy analysis. In Study 2, a total of 53 subjects were randomized. Of the 53 subjects, 51 subjects (25 in the 1 g/kg/day group, 26 in the 0.4 g/kg/day group) were included in the efficacy analysis, and the remaining 2 subjects was excluded from the analysis (1 subject whose parent withdrew informed consent and 1 subject with insufficient data).

The primary endpoint of Study 1 was the ordinal disability score.¹⁶ The median ordinal disability score was 2 at baseline in both treatment groups, and the worst score was 3 in the no-treatment group and 2 in the IVIG therapy group, showing no statistically significant difference between the groups ($P = 0.25$, Mann-Whitney test). The primary endpoint of Study 2 was the time required to regain the ability to walk independently. The median time [95% CI] was 7 [1, 18] days in the no-treatment group and 7 [1, 38] days in the IVIG therapy group, showing no statistically significant difference between the groups ($P = 0.94$, log-rank test).

In Study 1, adverse drug reactions were noted in 3 subjects in the IVIG therapy group (allergic reaction, headache, and hypertonia in 1 subject each). In Study 2, adverse drug reactions were noted in 18% of subjects in the 1 g/kg/day group and in 20% of subjects in the 0.4 g/kg/day group. The adverse drug reactions were allergic reaction, headache, and nausea (3 subjects each), pyrexia and white blood cell count decreased (2 subjects each), and proteinuria (1 subject).

7.3.9 *J Neurol Neurosurg Psychiatry. 2001;71:235-238 (CTD 5.4-30)*

A randomized, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of 3- or 6-day IVIG therapy in non-Japanese patients aged ≥ 16 years who had a confirmed diagnosis of GBS based on the criteria of Asbury et al. and were contraindicated from receiving PE therapy. Treatment was started within the first 30 days after symptom onset.

Immunoglobulin (0.4 g/kg/day) was administered intravenously once daily for 3 or 6 days.

A total of 39 randomized subjects (21 in the 3-day treatment group, 18 in the 6-day treatment group) were included in the safety and efficacy analyses.

The primary endpoint of the study was the time required to regain the ability to walk 5 m with support. The median time required to regain the ability to walk 5 m with support was 131 days in the 3-day treatment group and 84 days in the 6-day treatment group, showing no statistically significant difference between the groups ($P = 0.08$, Wilcoxon rank sum test).

Major adverse events were pyrexia (48% in the 3-day treatment group, 33% in the 6-day treatment group) and hypotension (5% in the 3-day treatment group, 17% in the 6-day treatment group).

¹⁵ Subjects who became unable to walk 5 m during Study 1 were allowed to be enrolled in Study 2.

¹⁶ 0, healthy; 1, able to run; 2, able to walk 5 m unaided; 3, able to walk 5 m with support; 4, unable to walk but able to lift legs; 5, unable to walk nor to lift legs; 6, requiring assisted ventilation

7.3.10 Ther Apher. 2000;4:198-200 (CTD 5.4-31)

A randomized, open-label, parallel group, comparative study was conducted to investigate the efficacy and safety of PE therapy, plasma absorption (PA) therapy, and combination of PA and IVIG therapies (PA + IVIG therapy) in non-Japanese patients who had a clinical diagnosis of GBS based on the criteria of Asbury et al.

Patients in the PE therapy group underwent plasma exchange (2.0 to 2.5 L), patients in the PA therapy group underwent plasma apheresis (1.5 to 3.7 L), and patients in the PA + IVIG therapy group underwent plasma apheresis, followed by IVIG therapy (intravenous immunoglobulin [0.4 g/kg/day] once daily for 5 days).

All 45 randomized subjects (11 in the PE therapy group, 13 in the PA therapy group, 21 in the PA + IVIG therapy group) were included in the safety and efficacy analyses.

The primary endpoint of the study was the change in FG score at 4 weeks. No statistically significant difference was observed in the change in FG score at 4 weeks between the PE therapy group and the PA therapy group (Wilcoxon-Mann-Whitney test). In contrast, a statistically significant difference was observed in the change in FG score between the combined data from the PE and PA therapy groups and the data from the PA + IVIG therapy group ($P = 0.02$, Wilcoxon-Mann-Whitney test).

No death occurred.

7.3.11 Ther Apher. 1998;2:288-291 (CTD 5.4-32)

A randomized, parallel group, comparative study was conducted to investigate the efficacy of IVIG therapy and PE therapy in non-Japanese patients with postinfectious polyneuritis (GBS and cranial neuritis).

All 15 randomized subjects (7 in the IVIG therapy group [of whom, 5 had GBS], 8 in the PE therapy group [of whom, 5 had GBS]) were included in the efficacy analysis.

The efficacy endpoint of the study was the proportion of subjects with improvement by ≥ 10 grades in muscle strength score¹⁷⁾ at 4 weeks. The proportion of such subjects was 40% in the IVIG therapy group and 60% in the PE therapy group, showing no statistically significant difference between the groups (Fisher's exact test).

7.3.12 Scand J Infect Dis. 1995;27:241-243 (CTD 5.4-34)

A randomized, parallel group, comparative study was conducted to compare the efficacy and safety of IVIG therapy to those of no-treatment in pediatric patients who were diagnosed with acute phase GBS.¹⁸⁾

Subjects in the IVIG therapy group received intravenous immunoglobulin (1 g/kg/day) once daily for ≥ 2 days.

All 18 randomized subjects (9 in the no-treatment group, 9 in the IVIG therapy group) were included in the efficacy and safety analyses.

The efficacy endpoint of the study was the time from onset to peak severity of symptoms. The mean time from onset to peak severity of symptoms was 12.5 days in the no-treatment group and 9.3 days in the IVIG therapy group. The mean time from peak severity to improvement of symptoms was 11.8 days in the no-treatment group and 7.5 days in the IVIG therapy group. A statistically significant difference was observed in both measures between the groups ($P < 0.05$, Mann-Whitney's U test).

¹⁷⁾ The strength of the following muscles was evaluated bilaterally according to 6 rating grades (0-5): Deltoid, biceps brachii, triceps brachii, wrist flexors, wrist extensors, quadriceps femoris, hamstrings, gastrocnemius, and tibialis anterior muscles; and total score (0-90) was calculated.

¹⁸⁾ Minimum required diagnostic criteria: Diminished motor function at ≥ 1 site, loss or clear reduction of reflex, and mononuclear cell count in the cerebrospinal fluid $\leq 10/\text{mm}^3$
Criteria strongly supporting the diagnosis: Progression lasting several days to more than several weeks, bilateral symptoms, mild symptoms with sensory organs, autonomic dysfunction, cranial nerve disorder, tendency of recovery 2 to 4 weeks after arrest of symptom progression

One death occurred in the no-treatment group.

7.R Outline of the review conducted by PMDA

7.R.1 Design of Japanese phase III study (CTD 5.3.5.2-1, Study NPB-01-13/C-01)

7.R.1.1 Appropriateness of open-label uncontrolled design of the study

PMDA asked the applicant to explain the appropriateness of the open-label uncontrolled design of the Japanese phase III study.

The applicant's explanation:

Conducting a placebo-controlled study was practically impossible for the following reasons: (i) GBS is a progressive disease, and (ii) freeze-dried sulfonated human normal immunoglobulin, a human immunoglobulin preparation of complete molecule form identical to Kenketu Glovenin-I, is approved for the treatment of "Guillain-Barré syndrome (for patients with severe GBS in the acute exacerbation phase and difficulty in walking)," although the two products are separately listed in the Minimum Requirements for Biological Products. Therefore, the applicant planned to demonstrate the efficacy and safety of Kenketu Glovenin-I by conducting a Japanese phase III study as an open-label, uncontrolled study and by using the efficacy and safety data of freeze-dried sulfonated human normal immunoglobulin and the data of IVIG therapy from foreign publications as reference data. To conduct the Japanese phase III study as an open-label, uncontrolled study, the proportion of patients showing improvement (39%) in the conventional therapy (including steroid therapy) group¹⁹⁾ in the foreign clinical study (CTD 5.4-7) was used as the threshold. Also, the Japanese phase III study was designed to demonstrate the efficacy of Kenketu Glovenin-I when the lower limit of 95% CI of the proportion of patients showing improvement in the Kenketu Glovenin-I group exceeded the above threshold. The target sample size was determined according to the following rationale: The proportion of patients showing improvement with Kenketu Glovenin-I treatment was assumed to be 70% based on the value observed in the Japanese study of freeze-dried sulfonated human normal immunoglobulin (CTD 5.4-17) (60.9%) and on the values in the foreign clinical studies of IVIG therapy (CTD 5.4-3, CTD 5.4-4) (80%, 69%, respectively), and the selected target sample size was 21 in order to ensure that the lower limit of 95% CI of the proportion of subjects showing improvement would equal to or exceed the above threshold (39%) with 80% statistical power. Thus, there should be no problem in conducting the Japanese phase III study as an open-label, uncontrolled study using a preset threshold to demonstrate efficacy.

7.R.1.2 Appropriateness of the inclusion criteria

PMDA asked the applicant to explain the appropriateness of the inclusion criteria employed in the Japanese phase III study.

The applicant's explanation:

The diagnostic criteria of Asbury et al. (CTD 5.4-1) have been widely used so far in clinical studies of GBS. The criteria include "progressive muscle weakness in 1 or more limbs" as a necessary diagnostic finding, but also state that if 1 limb is impaired, usually the contralateral limb is also impaired. Therefore, the above finding required for the diagnosis was modified to "progressive muscle weakness in 2 or more limbs" in the diagnostic criteria used in the Japanese phase III study (CTD 5.4-15). In the Japanese phase III study, the diagnosis was changed from GBS to CIDP for 2 subjects after the completion of treatment with Kenketu Glovenin-I, and these 2 subjects were excluded from the efficacy analysis. Symptoms relapsed in these subjects after the completion of treatment with Kenketu Glovenin-I, and the subjects were reassessed based on the electrophysiological findings and the time course of symptoms. As a result, they were determined to have been suffering from CIDP before the start of treatment with Kenketu Glovenin-I. If these 2 subjects were included in the efficacy analysis, the proportion of subjects [95% CI] showing improvement by ≥ 1 grade in FG score at 4 weeks would be 63.6% [40.7%, 82.8%] (14 of 22 subjects), with the lower limit of 95% CI exceeding the threshold (39%). This suggested that exclusion of these 2 subjects had only a minimal effect on efficacy evaluation.

¹⁹⁾ The best adjuvant therapy available at each study site at the time of study conduct was administered.

The inclusion criteria require that “patients be able to start the study drug within the first 2 weeks (up to 4 weeks) after symptom onset as a general rule,” for the following findings: symptoms reached peak severity within 7 days after onset in 34% of patients with GBS, within 14 days in 70% of patients with GBS, and within 21 days in 84% of patients with GBS, yet symptoms are progressively exacerbated up to approximately 4 weeks after onset (CTD 5.4-15). In light of the findings, the applicant considered treating patients within 14 days after onset (the time when symptoms reach the peak severity in most patients) was beneficial, and thus decided to start treatment “within the first 2 weeks after onset.” On the other hand, treating patients beyond 2 weeks after onset was also considered necessary because there are some cases where symptoms are progressively exacerbated up to approximately 4 weeks after onset. For this purpose, the wording of “up to 4 weeks” was added to the dosage regimen. In the Japanese phase III study, patients with a Hughes FG score of 3 were allowed to be enrolled if their symptoms were progressive. The term “progressive” means that the symptom of GBS has not reached peak severity and is expected to further progress if left untreated. The medical expert commented that physicians’ assessment of symptoms depends on the necessity of IVIG therapy in clinical practice, and that whether the symptoms are progressive and fall under an FG score of 3 is determined easily. Based on the comment, the inclusion of any specific criteria for such a case was considered unnecessary.

Based on the above, the applicant considered that the inclusion criteria employed in the Japanese phase III study were appropriate.

7.R.1.3 Appropriateness of the primary endpoint

PMDA asked the applicant to explain the appropriateness of the primary endpoint used in the Japanese phase III study.

The applicant’s explanation:

In the Japanese clinical study (CTD 5.4-17) of freeze-dried sulfonated human normal immunoglobulin, the time required to achieve improvement by 1 grade in FG score was used as the primary endpoint. However, in the Japanese phase III study, the primary endpoint was the proportion of subjects with improvement by ≥ 1 grade in Hughes FG score at Week 4 from baseline, for the following reasons:

- In the Japanese clinical study (CTD 5.4-17) of freeze-dried sulfonated human normal immunoglobulin, the proportion of subjects with improvement by ≥ 1 grade in FG score at 4 weeks was one of the secondary efficacy endpoints.
- In many foreign clinical studies of GBS as well, the proportion of subjects with improvement by ≥ 1 grade in FG score at 4 weeks was used as the efficacy endpoint [see “7.3 Clinical reports, etc.”].
- Improvement by 1 grade in FG score in patients with GBS who had an FG score of 4 or 5 or those with progressive GBS who had an FG score of 3, eligible patients in the Japanese phase III study, means that respiratory management is not necessary and that non-ambulatory patients become ambulatory. Therefore, improvement by ≥ 1 grade in FG score is clinically significant.

Based on the above, the applicant considers that the primary endpoint of the Japanese phase III study (the proportion of subjects with improvement by ≥ 1 grade in Hughes FG score from baseline at 4 weeks) is appropriate.

7.R.1.4 Appropriateness of the follow-up period

PMDA asked the applicant to explain the appropriateness of the follow-up period in the Japanese phase III study.

The applicant’s explanation:

In the Japanese phase III study, the follow-up period of 12 weeks was included after the end of treatment so that the data could be compared with those obtained in the Japanese clinical study (CTD 5.4-17) of freeze-dried sulfonated human normal immunoglobulin. Symptoms of GBS become exacerbated in a progressive manner up to approximately 4 weeks after onset, but then improve gradually over 3 to 12 months (CTD 5.4-16). In a study investigating changes in FG score in 100 patients with GBS (*J Neurol Neurosurg Psychiatry*. 1988;51:605-612), the mean FG score was 3.6 at 1 week after onset but 2.6 after 3 months. This suggests that symptoms improve in many patients at 12 weeks after the start of treatment, and therefore, no major changes in symptoms are likely to occur after ≥ 3 months. Recurrent GBS was experienced by only 2% to 5% of patients (CTD 5.4-16, *Intern Med*. 1995;34:1015-1018, etc.), and most

cases of relapses occurred after ≥ 10 years (*Intern Med.* 1995;34:1015-1018, The Research Project of the Specified Disease Treatment supported by the Health and Labour Sciences Research Grants, Study Group of Immunoneurological Diseases, 2002:116-117), precluding the follow-up until relapse. In the Japanese phase III study, therefore, neither long-term prognosis nor presence/absence of relapse was investigated. Based on the above, the applicant considers that the follow-up period included in the Japanese phase III study was appropriate.

PMDA's view:

The above explanation of the applicant is acceptable. Also, no major problems were found in the design of the Japanese phase III study. However, since the study was an open-label, uncontrolled study, the efficacy and safety of Kenketu Glovenin-I in patients with GBS should be evaluated based not only on the results of the Japanese phase III study but also on the efficacy and safety data of freeze-dried sulfonated human normal immunoglobulin and the efficacy and safety data of IVIG therapy from foreign publications [see "7.R.2 Efficacy of Kenketu Glovenin-I"].

7.R.2 Efficacy of Kenketu Glovenin-I

PMDA asked the applicant to explain the efficacy of Kenketu Glovenin-I, by also taking account of the efficacy and safety data of freeze-dried sulfonated human normal immunoglobulin and the data of IVIG therapy from foreign publications.

The applicant's explanation:

Table 1 shows the proportion of subjects with improvement by ≥ 1 grade in FG score from baseline at 4 weeks in the Japanese phase III study (CTD 5.3.5.2-1, Study NPB-01-13/C-01) and in published literature on IVIG therapy. The proportion of subjects with improvement in the Japanese phase III study (65.0%) was within the range found in the published literature (53%-81.8%). The proportion of subjects with improvement in the published literature excluding the use results survey of freeze-dried sulfonated human normal immunoglobulin (CTD 5.4-11) was 60.8% (186 of 306 subjects),²⁰⁾ which was not significantly different from the value obtained in the Japanese phase III study.

²⁰⁾ When the number of patients with improvement was not presented in the published literature, the number was calculated from the total number of subjects evaluated and the proportion of subjects with improvement.

Table 1. Proportion of subjects with improvement by ≥ 1 grade in FG score from baseline at 4 weeks in the Japanese phase III study and in published literature

Data	Group	Dosage regimen	No. of subjects evaluated	Proportion (No. of subjects with improvement)
Study NPB-01-13/C-01	Kenketu Glovenin-I	400 mg/kg/day for 5 days	20	65.0 (13)
CTD 5.4-3	IVIG therapy	500 mg/kg/day for 4 days	26	69 ^{a)}
	PE therapy	A total volume of 200 to 250 mL/kg of plasma was exchanged in 5 sessions over 7 to 10 days.	24	61 ^{a)}
CTD 5.4-4	IVIG therapy	400 mg/kg/day for 5 days	20	80.0 (16)
	PE therapy	Performed 5 sessions	21	71.4 (15)
	IAPP therapy	Performed 5 sessions	14	50.0 (7)
CTD 5.4-11	IVIG therapy	400 mg/kg/day for 5 days	First treatment 1097	69.4 (761)
			Second treatment 156	53.8 (84)
CTD 5.4-14	IVIG therapy	400 mg/kg/day for 5 days	74	53 ^{a)}
	PE therapy	A total volume of 200 to 250 mL/kg of plasma was exchanged in several sessions every 4 to 6 days.	73	34 ^{a)}
CTD 5.4-17	IVIG therapy	400 mg/kg/day for 5 days	23	60.9 (14)
	PE therapy	A total volume of 200 to 250 mL/kg of plasma was exchanged in up to 7 sessions over 4 weeks.	24	65.0 (13)
<i>Ital J Neurol Sci.</i> 1995;16:487-492 (CTD 5.4-33)	IVIG therapy	400 mg/kg/day for 5 days	12	58.3 (7)
	PE therapy	1900 mL exchanged	9	55.5 (5)
<i>Lancet.</i> 2004;363:192-6 (CTD 5.4-27)	IVIG therapy/ methylprednisolone	IVIG therapy (400 mg/kg/day for 5 days), followed by methylprednisolone 500 mg/day (8 mg/kg/day in children) or placebo administered intravenously for 5 days	112	67.9 (76)
	IVIG therapy/placebo		113	55.8 (63)
<i>Pediatr Int.</i> 2003;45:543-9 (CTD 5.4-28)	IVIG therapy	400 mg/kg/day for 5 days	11	81.8 (9)
<i>Neurological Therapeutics.</i> 2009;26:61-67 (CTD 5.4-38)	IVIG therapy	400 mg/kg/day for 5 days	27	74.1 ^{a)}
	IAPP therapy	Up to 7 days	23	43.5 ^{a)}

a) Number of subjects with improvement not described

The primary endpoint of the Japanese clinical study (CTD 5.4-17) of freeze-dried sulfonated human normal immunoglobulin was the time to improvement by 1 grade in FG score. The median time to improvement by 1 grade in FG score was 15.0 days in the Japanese phase III study of Kenketu Glovenin-I and 14 days in the clinical study (CTD 5.4-17) of freeze-dried sulfonated human normal immunoglobulin, showing no significant difference between the two studies.

Also, the above results showed that there was no significant difference between the efficacy of IVIG therapy in published literature and that of Kenketu Glovenin-I in the Japanese phase III study, demonstrating the efficacy of Kenketu Glovenin-I in the treatment of GBS.

PMDA's view:

In the Japanese phase III study which investigated the proportion of subjects with improvement by ≥ 1 grade in Hughes FG score from baseline at 4 weeks, the lower limit of the 95% CI of the observed proportion (40.8%) exceeded the preset threshold (39%). Also, results obtained in this study were similar to those reported in the published literature on IVIG therapy, demonstrating the efficacy of Kenketu Glovenin-I in the treatment of GBS.

7.R.3 Safety of Kenketu Glovenin-I

7.R.3.1 Difference in safety of Kenketu Glovenin-I between approved indications and GBS

PMDA asked the applicant to explain whether the safety of Kenketu Glovenin-I used for the treatment of GBS is different from that of Kenketu Glovenin-I used for the approved indications.

The applicant's explanation:

Table 2 summarizes major adverse events observed when Kenketu Glovenin-I was used for the approved indications and those observed in the Japanese clinical study of GBS. The incidences of headache,

hepatic enzyme increased, insomnia, and pneumonia aspiration were higher with GBS than those with the approved indications.

Table 2. Incidences of major adverse events in Japanese clinical studies of GBS and approved indications

	GBS	Bullous pemphigoid	SJS and toxic epidermal necrolysis	Pemphigus	Chronic inflammatory demyelinating polyradiculoneuropathy	Agammaglobulinemia or hypogammaglobulinemia	Severe infection	Idiopathic thrombocytopenic purpura	Kawasaki's disease
Code number of study or data submitted for approval	NPB-01-13/C-01	NPB-01-06/E-01 NPB-01-06/C-01	NPB-01-07/C-01	NPB-01-01/DC-01	G-1 G-2	VII-2	VII-3	G	G-1 G-2
No. of subjects evaluated	22	39	7	41	99	39	398	156	160
Adverse events	22 (100)	35 (89.7)	7 (100)	34 (82.9)	24 (24.2)	9 (23.1)	9 (2.3)	29 (18.6)	9 (5.6)
Major adverse events									
Headache	8 (36.4)	0	0	3 (7.3)	8 (8.1)	0	0	10 (6.4)	0
ALT increased	5 (22.7)	0	0	7 (17.1)	4 (4.0)	0	0	2 (1.3)	0
AST increased	5 (22.7)	0	0	4 (9.8)	4 (4.0)	0	0	2 (1.3)	0
Hepatic enzyme increased	5 (22.7)	0	0	0	0	0	0	0	0
Insomnia	4 (18.2)	1 (2.6)	0	3 (7.3)	0	0	0	0	0
Pneumonia aspiration	4 (18.2)	0	0	0	0	0	0	0	0
Pyrexia	3 (13.6)	5 (12.8)	0	4 (9.8)	4 (4.0)	16 (41.0)	2 (0.5)	5 (3.2)	4 (2.5)
Hepatic function abnormal	3 (13.6)	4 (10.3)	2 (28.6)	3 (7.3)	0	0	0	1 (0.6)	0
Anaemia	3 (13.6)	0	2 (28.6)	0	0	0	0	0	0
Nasopharyngitis	1 (4.5)	5 (12.8)	1 (14.3)	8 (19.5)	0	0	0	0	0
Bullous pemphigoid	0	7 (17.9)	0	0	0	0	0	0	0

Number of subjects with adverse events (incidence [%])

The applicant presented the following description of headache, hepatic enzyme increased, insomnia, and pneumonia aspiration observed, and claimed that no clinically significant safety events associated with the use of Kenketu Glovenin-I occurred in patients with GBS and that the risk of these adverse events would not exceed the risk associated with the use of Kenketu Glovenin-I for the approved indications.

- **Headache**

The incidence of headache was 70.0% (14 of 20 subjects) and 30.8% (8 of 26 subjects) in the Japanese clinical study of IVIG therapy (CTD 5.4-10, *Neurological Therapeutics*. 2002;19:415-420) and 5% to 20% in a foreign review article (*J Allergy Clin Immunol*. 2008;122:1238-1239). No clear tendency toward a higher incidence of headache was shown in the Japanese phase III study. In the same study, severe headache was not observed whereas moderate headache occurred in 2 subjects but resolved without any medical intervention or after treatment with an anti-inflammatory analgesic agent. Although the incidence of headache tended to be higher in subjects aged <65 years (58.3% [7 of 12 subjects]) than in subjects aged ≥65 years (10% [1 of 10 subjects]), the literature has already reported that IVIG therapy-associated headache tends to occur more frequently in younger subjects (*Neurological Therapeutics*. 2002;19:415-420). Since precautionary advice about headache has already been provided in the package insert, further advice is unnecessary.

- Hepatic enzyme increased
The incidence of hepatic dysfunction-related adverse events²¹⁾ in clinical studies ranged from 26.8% to 28.6% in the treatment of bullous pemphigoid, Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis, and pemphigus,²²⁾ while it was 63.6% in the treatment of GBS. Adverse events tended to occur in patients with GBS more frequently, but all of them were mild in severity. Also, a report shows that 35% to 38% of patients with GBS had hepatic dysfunction attributed to an antecedent infection, alcohol, or drugs before treatment, suggesting that the underlying disease has a significant effect on hepatic dysfunction in patients with GBS (*the Journal of the Japanese Society of Internal Medicine*. 2007;96:246-253). Furthermore, since precautionary advice about hepatic dysfunction and jaundice has already been provided in the package insert, further advice is unnecessary.
- Insomnia
Insomnia was reported by 4 subjects had in the Japanese phase III study of GBS. Of the 4 subjects, 3 had insomnia attributable to environmental change associated with hospitalization, and the remaining 1 experienced the symptom due to low back pain. A causal relationship to Kenketu Glovenin-I was ruled out in all of them. Therefore, the inclusion of precautionary advice about insomnia in the package insert is unnecessary.
- Pneumonia aspiration
GBS is often accompanied by bulbar palsy such as dysphagia and dyslalia (*Guillain-Barré syndrome*. F.A.Davis Company;1991:73-105). Thus, pneumonia aspiration was considered a GBS-related event and a causal relationship to Kenketu Glovenin-I was ruled out. Therefore, the inclusion of precautionary advice about pneumonia aspiration in the package insert is unnecessary.

7.R.3.2 Safety of Kenketu Glovenin-I versus freeze-dried sulfonated human normal immunoglobulin

PMDA asked the applicant to explain the safety of Kenketu Glovenin-I versus freeze-dried sulfonated human normal immunoglobulin in the treatment of GBS.

The applicant's explanation:

Table 3 shows the incidences of adverse drug reactions and laboratory abnormalities in the Japanese phase III studies of Kenketu Glovenin-I and of freeze-dried sulfonated human normal immunoglobulin. Results showed no significant difference in the incidences of laboratory abnormalities between the two therapies, whereas the incidences of adverse drug reactions other than laboratory abnormalities were higher with Kenketu Glovenin-I, but the reason for the observed difference was unclear. On the other hand, the incidence of adverse drug reactions or laboratory abnormalities was 62.5% (5 of 8 subjects) when freeze-dried sulfonated human normal immunoglobulin was administered to 6 patients with GBS and 2 patients with CIDP (*Jpn Pharmacol Ther*. 1997;7:967-974), showing no significant difference compared with the incidence of adverse drug reactions (including laboratory abnormalities) in the Japanese phase III study of Kenketu Glovenin-I (72.7%). Also, the incidence of skin disorder-related adverse drug reactions²³⁾ was higher in the Japanese phase III study of Kenketu Glovenin-I (27.3% [6 of 22 subjects]) than in the study of freeze-dried sulfonated human normal immunoglobulin (13.0% [3 of 23 subjects]). Although the cause of this difference is unclear, none of the skin disorder-related adverse drug reactions associated with the use of Kenketu Glovenin-I was serious. In addition, since precautionary advice about hypersensitivity has been included in the package insert, advice about skin disorder is considered unnecessary.

²¹⁾ Events coded to "Drug related hepatic disorders - comprehensive search" in Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA Queries (SMQ)

²²⁾ For chronic inflammatory demyelinating polyradiculoneuropathy, agammaglobulinemia or hypogammaglobulinemia, severe infection, idiopathic thrombocytopenic purpura, and Kawasaki's disease, subjects were not identified when adverse events were tabulated. Therefore, adverse events in these subjects were not compared with those in GBS patients.

²³⁾ Events coded to "Skin and subcutaneous tissue disorders" in MedDRA system organ class (SOC)

Table 3. Incidences of adverse drug reactions and laboratory abnormalities in Japanese phase III studies of Kenketu Glovenin-I and of freeze-dried sulfonated human normal immunoglobulin

	Kenketu Glovenin-I	Freeze-dried sulfonated human normal immunoglobulin
	Study NPB-01-13/C-01	Phase III study/comparative study ^{a)}
No. of subjects evaluated	22	23
Adverse drug reactions (excluding laboratory abnormalities)	14 (63.6)	5 (21.7)
Major events	Headache	1 (4.3)
	Pyrexia	1 (4.3)
	Drug eruption	0
	Rash	3 (13.0)
Laboratory abnormalities	9 (40.9)	10 (43.5)
Major events	ALT increased	4 (18.2)
	Hepatic enzyme increased	4 (18.2)
	AST increased	3 (13.6)
	White blood cell count decreased	2 (9.1)
	Eosinophil count decreased	1 (4.5)
	γ -GTP increased	0
	Cerebrospinal fluid cell count increased	0
	Granulocyte count decreased	0
	Protein urine present	0

Number of patients with adverse drug reactions (incidence [%])

a) Summary of application data of Kenketsu Venilon-I for extension of the indication to include GBS, <http://www.pmda.go.jp/drugs/2000/g001206/index.html>

7.R.3.3 Risk of aseptic meningitis

Taking account of aseptic meningitis reported in 1 subject in the Japanese phase III study, PMDA asked the applicant to explain the risk of aseptic meningitis in GBS patients.

The applicant's explanation:

Table 4 shows the incidence of aseptic meningitis-related adverse events²⁴⁾ reported in the Japanese clinical studies of Kenketu Glovenin-I treatment in patients with GBS, bullous pemphigoid, SJS and toxic epidermal necrolysis, and pemphigus.²⁵⁾ No severe or serious events were reported in any of the studies. There was no trend of difference in the time to onset of adverse events between studies. Furthermore, since precautionary advice about aseptic meningitis has already been provided in the package insert, further advice is considered unnecessary.

Table 4. Incidence of aseptic meningitis-related adverse events in Japanese clinical studies of Kenketu Glovenin-I in patients with GBS, bullous pemphigoid, SJS and toxic epidermal necrolysis, and pemphigus

	GBS	Bullous pemphigoid	SJS and toxic epidermal necrolysis	Pemphigus
	Study NPB-01-13/C-01	Study NPB-01-06/E-01 Study NPB-01-06/C-01	Study NPB-01-07/C-01	Study NPB-01-01/DC-01
No. of subjects evaluated	22	39	7	41
Aseptic meningitis-related adverse events	13 (59.1)	6 (15.4)	1 (14.3)	7 (17.1)
Headache	8 (36.4)	0	0	3 (7.3)
Pyrexia	3 (13.6)	5 (12.8)	0	3 (7.3)
Delirium	2 (9.1)	0	1 (14.3)	0
Loss of consciousness	1 (4.5)	0	0	0
Meningitis aseptic	1 (4.5)	0	0	0
Musculoskeletal stiffness	0	1 (2.6)	0	0
Body temperature increased	0	0	0	1 (2.4)

Number of subjects with adverse events (incidence [%])

PMDA's view:

The above explanation of the applicant is acceptable. The safety profile of Kenketu Glovenin-I in

²⁴⁾ Events coded to "Noninfectious meningitis" in MedDRA SMQ or to cluster headache, drug withdrawal headache, exertional headache, headache, head discomfort, medication overuse headache, postictal headache, premenstrual headache, procedural headache, tension headache, hemiplegic migraine, migraine, migraine with aura, migraine without aura, vascular headache, body temperature increased, hyperpyrexia, hyperthermia, pyrexia, sweating fever, or nuchal rigidity in preferred term (PT)

²⁵⁾ For chronic inflammatory demyelinating polyradiculoneuropathy, agammaglobulinemia or hypogammaglobulinemia, severe infection, idiopathic thrombocytopenic purpura, and Kawasaki's disease, subjects were not identified when adverse events were tabulated. Therefore, adverse events in these subjects were not compared with those in GBS patients.

patients with GBS is not significantly different from that in patients with diseases as the approved indications, nor from the safety profile of freeze-dried sulfonated human normal immunoglobulin. Since precautionary advice about the known risks of Kenketu Glovenin-I has already been provided in the package insert, further advice is unnecessary.

7.R.4 Clinical positioning and indication

PMDA asked the applicant to explain the clinical positioning of Kenketu Glovenin-I in the treatment of GBS and then to explain the appropriateness of the proposed indication.

The applicant's explanation:

Several Japanese and foreign textbooks (CTD 5.4-44, CTD 5.4-45, CTD 5.4-46), review articles (CTD 5.4-49), and guidelines (CTD 5.4-15, CTD 5.4-16) recommend IVIG therapy alone or IVIG and plasma perfusion (PP) therapies²⁶⁾ as the first-line therapy for GBS. Although no grounds for choosing either IVIG or PP therapy are clarified, the referenced documents state that IVIG therapy allows immediate initiation of the treatment without specific equipment while reducing physical burden on the patient, compared with PP therapy. Also, the Japanese textbook (CTD 5.4-44) and guideline (CTD 5.4-16) recommend the use of IVIG therapy in GBS patients with an FG score of ≥ 4 or progressive GBS patients with an FG score of 3. Since efficacy and safety are unlikely to significantly differ between Kenketu Glovenin-I and freeze-dried sulfonated human normal immunoglobulin [see "7.R.2 Efficacy of Kenketu Glovenin-I" and "7.R.3 Safety of Kenketu Glovenin-I"], Kenketu Glovenin-I may be positioned as a treatment option for patients with severe GBS in the acute exacerbation phase and difficulty in walking, as is the case with freeze-dried sulfonated human normal immunoglobulin. Taking account of the indications of freeze-dried sulfonated human normal immunoglobulin, adding "Guillain-Barré syndrome (for patients with severe GBS in the acute exacerbation phase and difficulty in walking)" to the indication of Kenketu Glovenin-I should be appropriate.

PMDA's view:

The above explanation of the applicant is acceptable. Kenketu Glovenin-I can be a treatment option for GBS in Japan. Also, on the basis of the patients investigated in the Japanese phase III study and of the indication of freeze-dried sulfonated human normal immunoglobulin, the indication proposed for Kenketu Glovenin-I should pose no problem.

7.R.5 Dosage and administration

PMDA asked the applicant to explain the appropriateness of the proposed dosage and administration.

The applicant's explanation:

While many Japanese and foreign textbooks and guidelines (CTD 5.4-15, CTD 5.4-16, CTD 5.4-44, CTD 5.4-48, CTD 5.4-49) recommend 400 mg/kg/day for 5 days as the dosage regimen for IVIG therapy, a foreign textbook (CTD 5.4-47) recommends 2 g/kg/day for 2 to 5 days, but the total dose used in the latter regimen is similar to that in the former regimen. The dosage regimen employed in the Japanese phase III study (CTD 5.3.5.2-1, Study NPB-01-13/C-01) of Kenketu Glovenin-I was 400 mg/kg/day by intravenous infusion for 5 consecutive days, and this regimen was selected based on the approved dosage and administration for freeze-dried sulfonated human normal immunoglobulin (intravenous infusion or intravenous injection of 400 mg/kg/day for 5 days). Since the efficacy and safety of Kenketu Glovenin-I was demonstrated in the Japanese phase III study using the above dosage and administration, the selected dosage and administration of Kenketu Glovenin-I (400 mg/kg/day by intravenous infusion for 5 consecutive days) was considered appropriate.

PMDA's view:

Taking account of the results of the Japanese phase III study and of the descriptions in Japanese and foreign textbooks, guidelines, etc., the proposed dosage and administration should pose no particular problem.

²⁶⁾ PE (double membrane filtration) or IAPP

7.R.6 Retreatment after relapse

Since GBS may relapse after the improvement of symptoms, PMDA asked the applicant to explain the efficacy and safety of Kenketu Glovenin-I used for retreatment of relapsed GBS.

The applicant's explanation:

The Japanese phase III study (CTD 5.3.5.2-1, Study NPB-01-13/C-01) did not plan to use Kenketu Glovenin-I for retreatment of relapsed GBS or evaluate its efficacy and safety in such a use. The Japanese clinical practice guideline (CTD 5.4-16) states that a repeated IVIG therapy should be considered when symptoms relapse after improvement with the first IVIG therapy. The foreign clinical practice guidelines (CTD 5.4-48, CTD 5.4-49) also recommend repeated IVIG therapy if symptoms relapse after the first IVIG therapy. The package insert of freeze-dried sulfonated human normal immunoglobulin states that, in the event of relapse, appropriate measures including retreatment with the drug should be considered. The use results survey of freeze-dried sulfonated human normal immunoglobulin in patients with GBS showed that retreatment with the same dosage regimen as the first therapy was similarly effective if given early after the first therapy, and that the retreatment did not cause any increase in adverse drug reactions (CTD 5.4-11). In the Japanese phase III study of Kenketu Glovenin-I, retreatment with IVIG therapy, PE therapy, or corticosteroid was allowed as a rescue therapy if FG remained unchanged or worsened from baseline at more than 2 weeks after the end of treatment and if retreatment was deemed necessary by the investigator (or subinvestigator). Among subjects who failed to achieve improvement after the first dose of Kenketu Glovenin-I and received rescue therapy, 1 subject received Kenketu Glovenin-I as the rescue therapy. This subject achieved improvement by 1 grade in FG score after the rescue therapy. Eczema asteatotic occurred in the subject after the rescue therapy, but it was mild. Based on the above, precautionary advice should be provided in the package insert, so that appropriate measures, including retreatment with Kenketu Glovenin-I, should be considered in the event of relapse.

PMDA's view:

Given the limited information available on the efficacy and safety of Kenketu Glovenin-I used for retreatment in patients with GBS, and based on the descriptions in the Japanese and overseas clinical practice guidelines and in the package insert of freeze-dried sulfonated human normal immunoglobulin, precautionary advice should be given in the package insert to ensure that appropriate measures, including retreatment with Kenketu Glovenin-I, are considered in the event of relapse.

7.R.7 Post-marketing investigations

PMDA's view:

On the basis of the results of the clinical studies of Kenketu Glovenin-I, the efficacy and safety data of freeze-dried sulfonated human normal immunoglobulin, and the data of IVIG therapy from foreign publications, no new safety concerns are found in the risk management plan pertaining to the present application. No additional pharmacovigilance activities or risk minimization activities are necessary at this point.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The assessment is currently ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The inspection is currently ongoing. Results and PMDA's conclusion will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of Review Report (1)

PMDA has concluded that the data submitted demonstrate the efficacy of Kenketu Glovenin-I in the treatment of patients with Guillain-Barré syndrome (for patients with severe GBS in the acute exacerbation phase and difficulty in walking), and acceptable safety in view of the benefits indicated by

the data submitted. Kenketu Glovenin- offers a new treatment option for patients with GBS and its use for the new indication is of clinical significance.

PMDA has concluded that Kenketu Glovenin-I may be approved if Kenketu Glovenin-I is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 10, 2016

Product Submitted for Approval

Brand Name	Kenketu Glovenin-I for I.V. Injection 500 mg, Kenketu Glovenin-I 2500 mg, Kenketu Glovenin-I 5000 mg
Non-proprietary Name	Freeze-dried Polyethylene Glycol-treated Human Normal Immunoglobulin
Applicant	Nihon Pharmaceutical Co., Ltd.
Date of Application	November 5, 2015

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized in the following. The expert advisors present during the Expert Discussion were nominated based on their declarations etc., concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc., by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA's conclusions on issues presented in the Review Report (1) and the conclusion that no additional pharmacovigilance activities or risk minimization activities are necessary.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.2-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed that the clinical study as a whole was conducted in compliance with GCP. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. The following findings were identified at some of the participating medical institutions and the sponsor, although they did not significantly affect the overall evaluation of the study. These findings requiring corrective actions were notified to the head of the pertinent medical institutions and the applicant (sponsor).

[Findings requiring corrective action]

Medical institutions

- Inconsistencies between source data and case report forms (inconsistencies in electrophysiological findings and manual muscle test scores)

Sponsor

- Failure to appropriately identify the inconsistencies between source data and case report forms (inconsistencies in electrophysiological findings and manual muscle test scores) by monitoring

3. Overall Evaluation

As a result of its regulatory review, PMDA has concluded that Kenketu Glovenin-I may be approved for the indication and dosage and administration shown below.

Indications

1. Agammaglobulinemia or hypogammaglobulinemia
2. Coadministration with antibiotics for the treatment of severe infection
3. Idiopathic thrombocytopenic purpura (ITP) (for patients with ITP unresponsive to other drugs who have a marked bleeding tendency and who require temporary hemostasis during emergency procedures including surgery and delivery)
4. Kawasaki's disease (KD) in the acute phase (for patients with severe KD who have a risk of coronary artery disorder)
5. Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy)
6. Pemphigus (for patients with pemphigus inadequately responsive to corticosteroids)
7. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (for patients with SJS or TEN inadequately responsive to corticosteroids)
8. Bullous pemphigoid (BP) (for patients with BP inadequately responsive to corticosteroids)²⁷⁾
9. Guillain-Barré syndrome (GBS) (for patients with severe GBS in the acute exacerbation phase and difficulty in walking)

(Underline denotes additions.)

Dosage and Administration

Kenketu Glovenin-I should be reconstituted with the supplied solvent (Water for Injection [the Japanese Pharmacopoeia]) to a concentration of 500 mg/10 mL. The reconstituted solution should be administered according to the regimens specified below for each indication. Direct intravenous injection should be given at a very slow rate.

Agammaglobulinemia or hypogammaglobulinemia:

The usual dosage for human immunoglobulin G is 200 to 600 mg (in 4-12 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection once every 3 to 4 weeks. The dose may be adjusted according to the patient's condition.

Coadministration with antibiotics for the treatment of severe infection:

The usual dosage of human immunoglobulin G is 2500 to 5000 mg (in 50-100 mL) for adults, and 100 to 150 mg (in 2-3 mL)/kg body weight for children, administered by an intravenous infusion or a direct intravenous injection. The dose may be adjusted according to the patient's condition.

Idiopathic thrombocytopenic purpura:

The usual daily dosage of human immunoglobulin G is 200 to 400 mg (in 4-8 mL)/kg body weight administered by an intravenous infusion or a direct intravenous injection. If symptoms do not improve after 5-day intravenous immunoglobulin treatment, the treatment should be discontinued. The dose may be adjusted according to the patient's age and condition.

²⁷⁾ The partial change application for extension of the indication to include "bullous pemphigoid (BP) (for patient with BP inadequately responsive to corticosteroids)" was approved on November 20, 2015 after submission of the present application.

Kawasaki's disease in the acute phase:

The usual dosage of human immunoglobulin G is 200 mg (in 4 mL)/kg body weight administered once daily for 5 days by an intravenous infusion or a direct intravenous injection, or 2000 mg (in 40 mL)/kg body weight administered by a single intravenous infusion. The dose for 5-day administration may be decreased or increased according to the patient's age and condition, and the dose for single-dose administration may be decreased according to the patient's age and condition.

Improvement of muscle weakness in patients with chronic inflammatory demyelinating polyradiculoneuropathy (including multifocal motor neuropathy)

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion or a direct intravenous injection. The dose may be decreased according to the patient's age and condition.

Pemphigus:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion. The dose may be decreased according to the patient's age and condition.

Stevens-Johnson syndrome and toxic epidermal necrolysis:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

Bullous pemphigoid²⁷⁾:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

Guillain-Barré syndrome:

The usual dosage of human immunoglobulin G is 400 mg (in 8 mL)/kg body weight administered once daily for 5 consecutive days by an intravenous infusion.

(Underline denotes additions.)