Clinical Study Protocol

NCT Number: NCT05084053

Title: A Phase 3 Study to Evaluate the Efficacy, Safety and Tolerability of TAK-771 for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN) in Japanese Subjects

Study Number: TAK-771-3002

Document Version and Date: Amendment 3 / 27-Mar-2024

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

TAKEDA PHARMACEUTICALS

PROTOCOL: TAK-771-3002

Title:	A Phase 3 Study to Evaluate the Efficacy, Safety and Tolerability of TAK-771 for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN) in Japanese Subjects
Short Title:	A Study to Evaluate the Efficacy, Safety and Tolerability of TAK-771 for CIDP and MMN in Japanese Subjects
Sponsor:	Takeda Pharmaceutical Company Limited 1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, Japan
Study Number:	TAK-771-3002
IND Number:	Not Applicable **EudraCT Number:** Not Applicable
Compound:	TAK-771, 10% Immune Globulin Infusion (Human) [10% IGI] and Vorhyaluronidase Alfa (Genetical Recombination) [rHuPH20]
Date:	27 Mar 2024 **Version/ Amendment Number:** Amendment 3

Amendment History:

Date	Amendment Number	Region
27 Mar 2024	Amendment 3	Japan
18 May 2022	Amendment 2	Japan
16 Aug 2021	Amendment 1	Japan
31 Mar 2021	Original	Japan

1. ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

A separate contact information list will be provided to each site.

Takeda Development Center sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject.

General advice on protocol procedures should be obtained through the monitor assigned to the study site. Information on service providers is given and relevant guidelines provided to the site.

1.2 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.
- After obtaining the marketing authorization of this drug in Japan, this clinical trial will continue as a post-marketing clinical trial, and will comply with the GCP Ministerial Ordinance and the Ministerial Ordinance on the criteria for conducting post-marketing surveillance and testing of pharmaceuticals. After the transition to post-marketing clinical trials, the term “clinical trial” in the “clinical trial protocol” will be replaced with “post-marketing clinical trial”.

SIGNATURES

The signature of the responsible Takeda medical officer can be found on the signature page.

[redacted]

1.3 SUMMARY OF CHANGES FROM PREVIOUS PROTOCOL VERSION

The following is a summary of the changes made in the amendment 3:

- The description of the IgG subclass was removed in Section 9.1.9.
- The amount of blood drawing for anti-rHuPH20 antibodies and the maximum total amount of blood drawing per visit were modified due to the change of blood sampling tube used for anti-rHuPH20 antibodies test in Section 9.1.9 and Appendix A.
- The description of the timing of the neutralizing antibody measurement and binding antibody measurement was updated in Section 9.1.9.4.
- A supplementary explanation was added to Section 9.1.9.9, stating that antibody elution test will be optional if direct Coombs test for subjects who were suspected to have hemolytic anemia was positive.
- In Section 9.1.10.1, the description of contraceptive methods not available in Japan was removed.
- The analysis method for secondary endpoints was modified in Section 13.1.3.2.
- The information of web links for a couple of references listed (number 8 and 56) were updated based on the current availability in Section 16.

1.4 INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure, package insert and any other product/device-used-in-clinical-trial information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.2 of this protocol.
- Terms outlined in the study site agreement.
- Responsibilities of the Investigator (Appendix B).

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

TABLE OF CONTENTS

List of Tables

List of Figures

List of Appendix Tables

[redacted]

2. STUDY SUMMARY

Name of Sponsor(s): Takeda Pharmaceutical Company Limited	**Compound:** TAK-771	
Title of Protocol: A Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of TAK-771 for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Multifocal Motor Neuropathy (MMN) in Japanese Subjects	**IND No.:** Not applicable	EudraCT No.: Not applicable
Study Number: TAK-771-3002	**Phase:** 3	

Study Design:

This is a Phase 3, prospective, multicenter, open-label, non-controlled, single-arm study. There are two Epochs, with two cohorts for CIDP and MMN patients in this study. Investigational product (IP) administration and site visit schedule are the same in Cohort 1 and Cohort 2, but primary endpoints differ.

Subjects with confirmed CIDP or MMN who have remained on stable dosing regimen (monthly equivalent dose of 0.4 to 2.4 g/kg body weight [BW] with a dosing interval of 2 to 6 weeks) of intravenous immunoglobulin (IVIG) therapy for at least 12 weeks prior to screening will be enrolled in the study.

After informed consent is obtained, subjects will undergo screening and baseline procedures for the determination of eligibility and will continue to receive their own IVIG treatment at the same dose and dosing interval as prescribed prior to entry into this study.

Eligible subjects will receive TAK-771 SC for a treatment period of 6 months in Epoch 1. The IgG dose of TAK-771 per month will be adjusted to be equivalent to subject's monthly IVIG dose. The number of infusion visits and site visits during the SC treatment period will vary across subjects depending on whether their infusion cycles are every 2, 3, or 4 weeks. If a subject with CIDP has met relapse criteria or a subject with MMN has been judged as being worsened by the investigator/worsening criteria of CIDP/MMN during Epoch 1, the subject will be discontinued from the study treatment.

For safety and tolerability data, the sponsor set the minimum duration of Epoch 2 as 6 months. After the first 6 months of Epoch 2, if the subject is tolerating the drug well and voluntarily wishes to continue TAK-771 treatment, the subject can stay in the study until the commercial TAK-771 is available in each study site. After the first 6 months of Epoch 2, the investigator may adjust the dose of TAK-771 administration in every 3 months.

Primary Objectives:

To evaluate the efficacy of TAK-771 in Epoch 1 as a maintenance therapy for Japanese patients with CIDP and MMN to prevent relapse or progression of motor function.

Secondary Objectives:

1. To assess the safety and tolerability of TAK-771 in Epoch 1 and Epoch 2 as a maintenance therapy for Japanese patients with CIDP and MMN.
2. To assess the efficacy of TAK-771 in Epoch 1 and Epoch 2.

Subject Population: Subjects with a confirmed diagnosis of CIDP or MMN who have remained on a stable dosing regimen (monthly equivalent dose of 0.4 to 2.4 g/kg BW with a dosing interval of 2 to 6 weeks) of IVIG therapy for at least 12 weeks prior to screening.

Number of Subjects: Total: 21 subjects (as treated with TAK-771) [CIDP: 16 subjects (Cohort 1) , MMN: 5 subjects (Cohort 2)]	**Number of Sites:** Approximately 15 clinical sites planned, located in Japan

Dose Level(s): 80 U/g IgG (rHuPH20 drug product: 160 U/mL) Immunoglobulin infusion (IGI) 10%: the total amount of IgG administered per month will be the equivalent of that of previous IVIG treatment.	**Route of Administration:** SC infusion of rHuPH20 solution at a dose of 80 U/g IgG will be administered first, followed by SC infusion of 10% IGI within 10 minutes of completion of the infusion of rHuPH20 solution.
Duration of Treatment: Approximately 45 months at the longest (until the commercial TAK-771 is available in each study site or study termination by the sponsor or regulatory agencies)	**Period of Evaluation:** • Screening: up to 8 weeks • SC treatment Epoch 1: 6 months • SC treatment Epoch 2: 6 months at minimum. Subjects can continue TAK-771 until the commercial TAK-771 is available in each study site or study termination by the sponsor or regulatory agencies.

Main Criteria for Inclusion:

A subject will be included in the study if he/she meets ALL following criteria to enroll in the study:

- The subject is a Japanese male or female aged ≥18 years old at the time of screening
- Subject has a documented diagnosis of definite or probable CIDP (focal atypical CIDP and pure sensory atypical CIDP will be excluded) or definite or probable MMN, as confirmed by a neurologist specializing/experienced in neuromuscular diseases to be consistent with the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria.
- Subject has responded to IgG treatment in the past (partial or complete resolution of neurological symptoms and deficits), and must currently be on stable doses of IVIG treatment within the dose range equivalent to a cumulative monthly dose of 0.4 to 2.4 g/kg BW (inclusive) administered intravenously for at least 12 weeks prior to screening. The dosing interval of IVIG treatment must be between 2 and 6 weeks (inclusive). Variations in the dosing interval of up to ±7 days or monthly dose amount of up to ±20% between subject's pre-study IgG infusions are within acceptable limits.
- CIDP subjects only - INCAT disability score between 0 and 7 (inclusive). Subjects with INCAT scores of 0, 1 (whether from upper or lower extremities), or 2 (if at least 1 point is from an upper extremity) at screening and/or baseline will be required to have a history of significant disability as defined by an INCAT disability score of 2 (must be exclusively from the lower extremities) or greater documented in the medical record.

Main Criteria for Exclusion:

A subject will be excluded from the study if he/she meets ANY of the following criteria.

CIDP patients

- Subjects with focal atypical CIDP or pure sensory atypical CIDP or multifocal acquired demyelinating sensory and motor neuropathy (MADSAM)
- Subjects with any neuropathy of other causes, including:
  a. Hereditary demyelinating neuropathies, such as hereditary sensory and motor neuropathy (HSMN) (Charcot-Marie-Tooth [CMT] disease), and hereditary sensory and autonomic neuropathies (HSANs).
  b. Neuropathies secondary to infections, disorders, or systemic diseases such as Borrelia burgdorferi infection (Lyme disease), diphtheria, systemic lupus erythematosus, POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, lymphoma, and amyloidosis.
  c. Multifocal motor neuropathy (MMN).
  d. Drug-, biologic-, chemotherapy-, or toxin-induced peripheral neuropathy.

MMN patients

- Subject with other neuropathies (eg, diabetic, lead, porphyric or vasculitic neuropathy, chronic inflammatory demyelinating polyradiculoneuropathy, Lyme neuroborreliosis, post radiation neuropathy, hereditary neuropathy with liability to pressure palsies, CMT neuropathies, meningeal carcinomatosis).

CIDP/MMN patients

- Subject with immunoglobin M (IgM) paraproteinemia, including IgM monoclonal gammopathy with high titer antibodies to myelin-associated glycoprotein.
- Subject with presence of prominent sphincter disturbance.
- Subject with any central demyelinating disorders such as multiple sclerosis.
- Subject with any chronic or debilitating disease, or central nervous disorder that causes neurological symptoms or may interfere with assessment of endpoint measures, including (but not limited to) arthritis, stroke, Parkinson's disease, and diabetic peripheral neuropathy.
- Subject with congestive heart failure (New York Heart Association [NYHA] class III/IV), unstable angina, unstable cardiac arrhythmias, or uncontrolled hypertension (defined as diastolic blood pressure >100 mmHg and/or systolic blood pressure >160 mmHg).
- Subjects with a history of deep vein thrombosis or thromboembolic events (eg, cerebrovascular accident, pulmonary embolism) within 12 months prior to screening.
- Subjects with condition(s) which could alter protein catabolism and/or IgG utilization (eg, protein-losing enteropathies, nephrotic syndrome).
- Subjects with a known history of chronic kidney disease, or glomerular filtration rate of <60 mL/min/1.73m^2 estimated based on the Chronic Kidney Disease Epidemiology Collaboration equation at the time of screening.
- Subjects with active malignancy requiring chemotherapy and/or radiotherapy, or history of malignancy with less than 2 years of complete remission prior to screening. Exceptions to this exclusion are: adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and stable prostate cancer not requiring treatment.
- Subject with clinically significant anemia that precludes repeated blood sampling during the study, or hemoglobin (Hgb) level of <10.0 g/dL at the time of screening.
- Subject with a known history of hypersensitivity or adverse reaction (ARs) such as urticaria, breathing difficulty, severe hypotension, or anaphylaxis following administration of human blood products such as human IgG, albumin, or other blood components.
  Note: Clinically non-significant skin reactions, as per the investigator's and the sponsor medical monitor's discretion, do not meet this exclusion criterion. Clinically non-significant skin reactions may include local reactions to injection such as injection site's itching, redness, erythema, or swelling.
- Subject has a known allergy to hyaluronidase of human (including recombinant human hyaluronidase) or animal origin such as bee or wasp venom.
- Subject with immunoglobulin A (IgA) deficiency and antibodies against IgA and a history of hypersensitivity
- Subject with abnormal laboratory values at screening meeting any one of the following criteria:
  a. Serum aspartate aminotransferase and alanine aminotransferase >2.5 × upper limit of normal.
  b. Platelet count <100,000 cells/µL.
  c. Absolute neutrophil count <1000 cells/µL.
- Subject has a known history of or is positive at screening for one or more of the following: hepatitis B surface antigen (HBsAG), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2.
- Subject has received or is currently receiving treatment with immunomodulatory/immunosuppressive agents within 6 months prior to screening.

- Subject has received or is currently receiving treatment with any corticosteroids dose within 8 weeks prior to screening, regardless of indication.
- Subject has undergone plasma exchange (PE) within 3 months prior to screening.
- Subject with acquired or inherited thrombophilic disorders. These will include the specific types of acquired or inherited thrombophilic disorders that could put subjects at risk of developing thrombotic events.

Main Criteria for Evaluation and Analyses:

Criteria for Evaluation and Analyses:

Primary Endpoint

Cohort 1 (CIDP)

Occurrence of relapse in Epoch 1 (worsening of functional disability defined as an increase of ≥1 point relative to the pre-SC treatment baseline score in adjusted INCAT disability score).

Cohort 2 (MMN)

Change in maximum grip strength in the more affected hand in Epoch 1 (per baseline measurement point, investigators judges which of both hands is more affected).

Secondary Endpoint

Safety

Cohort 1 (CIDP) and Cohort 2 (MMN)

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) regardless of causality.
- Causally related SAEs and/or AEs.
- Serious and/or nonserious ARs plus suspected ARs.
- Treatment-emergent SAEs and/or AEs associated with infusions, regardless of causality
- Causality of related SAEs and/or AEs associated with infusions
- AEs temporally associated with infusions (defined as AEs occurring during or within 72 hours after completion of an infusion)
- Serious and/or nonserious ARs plus suspected ARs associated with infusions
- Treatment-emergent systemic AEs associated with infusions
- Treatment-emergent local infusion site reactions associated with infusions
- Infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs.
- Development positive titer (≥160) binding antibodies, or develop neutralizing antibodies, to rHuPH20.

Efficacy

Cohort 1 (CIDP)

- CIDP worsening in Epoch 1 (defined as a ≥8 kPa decrease in the hand grip strength in the more affected hand) OR ≥4 points decrease in Rasch Built Overall Disability Scale (R-ODS) relative to the pre-SC treatment baseline score at 2 consecutive time points (at the time of withdrawal from the SC treatment period).
- Time to relapse in Epoch 1 and Epoch 2.
- Change from pre-SC treatment baseline in R-ODS score in Epoch 1.
- Change from baseline in an average of handgrip strength of both hands in Epoch 1.

Cohort 2 (MMN)

- Medical Research Council (MRC) sum score in Epoch 1.
- Guy's Neurological Disability Scale (GNDS) in upper limb and lower limb categories in Epoch 1.
- Change from baseline in an average of handgrip strength of both hands in Epoch 1.

Statistical Considerations:

Analysis of Primary Endpoint (CIDP)

The proportion of subjects with relapse and corresponding exact 2-sided Clopper-Pearson 95% confidence interval (CI) will be provided based on the full analysis set (FAS). Missing outcomes will be imputed as no relapse. The efficacy would be shown in the case that the upper bound of CI would be below the threshold of 57%.

Analysis of Primary Endpoint (MMN)

The mean change from baseline in maximum grip strength will be presented for more affected hand using descriptive statistics and 2-sided 95% CI based on the FAS. A detailed explanation for how to handle missing data and intercurrent event will be described in the statistical analysis plan. Descriptive statistics will be performed for all safety and tolerability outcome measures.

Although efficacy data will be assessed for CIDP and MMN independently, safety will be assessed as integrated data from CIDP and MMN subjects. Data for the 2 Epochs will be presented separately.

Sample Size Justification:

Cohort 1 (CIDP)

A recent meta-analysis reported that 43% of placebo-treated patients showed no deterioration in 5 placebo-controlled clinical studies, hence the estimated relapse rate in placebo-treated patients of 57%. The estimated relapse rate of Cohort 1 is 12% based on the average relapse rate in 2 clinical trials (13% in ICE study and 10% in the PATH extension study). Assuming a relapse rate of 12% and a dropout rate of 15%, the sample size of 16 subjects provides 90% power to demonstrate relapse rate that is significantly lower than 57% using a 95% two-sided Clopper-Pearson CI. This sample size was calculated based on simulation results from 100,000 trials.

Cohort 2 (MMN)

The target number of MMN subjects was determined based on feasibility given the inclusion and exclusion criteria for this study. Multifocal motor neuropathy is less prevalent than CIDP. The annual number of MMN patients in Japan is estimated to be about 400 cases. Five subjects are scheduled to be included in this study. Since this study is planned to be conducted in parallel with the clinical trial of maintenance therapy with CIDP patients, an effort would be made to recruit additional subjects until enrollment period of CIDP study ends, even if enrollment of 5 subjects is completed.

3. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	antibody detection assay
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BW	body weight
B19V	Parvovirus B19
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
CMT	Charcot-Marie-Tooth
eCRF	electronic case report form
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
EFNS	European Federation of Neurological Societies
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAV	hepatitis A virus
HBV	hepatitis B virus
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
Hgb	Hemoglobin
HYAL	Hyaluronidase
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IgA	immunoglobulin A
IgG	immunoglobulin G
IGI	immunoglobulin infusion
INR	international normalized ratio

Abbreviation	Definition
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IVIG	Intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
MMN	multifocal motor neuropathy
MRC	Medical Research Council
PE	plasma exchange
PID	primary immunodeficiency disease
PNS	Peripheral Nerve Society
PPS	per protocol set
PTE	pretreatment event
RNA	ribonucleic acid
R-ODS	Rasch-Built Overall Disability Scale
SAE	serious adverse event
SAP	statistical analysis plan
SC	Subcutaneous
SCIG	subcutaneous immunoglobulin
SD	standard deviation
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reactions
TEAE	Treatment-emergent adverse event
TIBC	total iron binding capacity
ULN	upper limit of normal
WOCBP	woman of childbearing potential

3.1 Corporate Identification

TDC Japan	Takeda Development Center Japan
TDC Asia	Takeda Development Center Asia, Pte Ltd
TDC Europe	Takeda Development Centre Europe Ltd.
TDC Americas	Takeda Development Center Americas, Inc.
TDC	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable
Takeda	TDC Japan, TDC Asia, TDC Europe and/or TDC Americas, as applicable

4. INTRODUCTION

4.1 Background

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired progressive chronic sensory and motor neuropathy with a relapsing and remitting or progressive course of more than 2 months, characterized by proximal weakness, positive sensory symptoms, areflexia without wasting, and impaired sensation with a preferential loss of vibration or joint position sense (European Federation of Neurological Societies, 2010, Köller et al., 2005).

While CIDP can occur in all ages, it occurs more often in the middle-aged and elderly population with a male predominance (Hughes, 2003). The peak incidence of CIDP is between the ages of 30 to 60 years (Dalakas, 2011). Approximately 60% of patients have a chronic progressive form and are typically older. Approximately 30% have a relapsing remitting course and these patients tend to be younger.

According to the nationwide survey by the Refractory Peripheral Neuropathy Study Group of Japan, the prevalence rate of CIDP in Japanese population per 100,000 was 1.61; 2.01 in males and 1.23 in females. The sex and age dependent prevalence rates were 0.22 in males and 0.24 in females in juveniles, 1.81 in males and 1.19 in females in young adults, and 3.12 in males and 1.64 in females in elderly adults.

These data demonstrated that the prevalence and incidence rates in Japanese population were similar to those reported in the Caucasian population. The pathogenic background is suggested to be common throughout the different races and geographic areas, while gender and age effects should be taken into account in the pathogenesis of CIDP (Iijima et al., 2008).

Multifocal motor neuropathy (MMN) is an immune-mediated demyelinating neuropathy characterized by asymmetric muscle weakness, predominantly of the upper limbs (European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy:, 2010, van Asseldonk et al., 2005, Vlam et al., 2012). Men are more commonly affected as compared to women with a ratio of 2.6:1 (van Asseldonk et al., 2005, Vlam et al., 2012). In most patients, the first symptoms occur between age 20 and 50 years (van Asseldonk et al., 2005).

In Japanese population, the prevalence was estimated to be 0.3 cases for MMN cases per 100,000 persons. The mean onset age was 42.2 years and sex dependent prevalence rates were 0.73 in males and 0.28 in females. Although the prevalence of MMN is low in Japan, it is mostly similar with that in other geographical areas in terms of sex ratio and age of onset (Matsui, 2012).

4.1.1 Indication and Current Treatment Options

CIDP

Treatment is recommended for all CIDP patients who demonstrate significant clinical symptoms in order to prevent continuing demyelination and secondary axon loss leading to permanent disability (Köller et al., 2005).

Conventional therapy for CIDP includes corticosteroids, plasma exchange (PE), and intravenous immunoglobulin (IVIG). Intravenous immunoglobulin has been the most studied treatment and the only approved therapy for CIDP for both induction and maintenance therapy. In clinical guidelines for treatment of CIDP, corticosteroids (Eftimov et al., 2012, Hughes et al., 2001, Nobile-Orazio et al., 2012, van Schaik et al., 2010) and PE (Dyck et al., 1986, Hahn et al., 1996, Mehndiratta and Hughes, 2012) are also first-line therapies for induction therapy and maintenance therapy (European Federation of Neurological Societies, 2010, Patwa et al., 2012). However, while corticosteroids are effective in treating the symptoms of CIDP, there are significant problems with safety and tolerability associated with corticosteroid treatment, particularly when given chronically (Gorson, 2012).

Adding an immunosuppressant or immunomodulatory drug may be considered, but there is insufficient evidence to recommend a particular immunosuppressant/immunomodulatory agent (Cocito et al., 2011, European Federation of Neurological Societies, 2010).

As an alternative option of IVIG, subcutaneous immunoglobulin (SCIG) replacement therapy is considered to be effective, safe, and also highly appreciated by patients (Misbah et al., 2009, Nicolay et al., 2006) and to have a low risk of systemic adverse reactions (ARs) (Gardulf et al., 1995, Gardulf et al., 1993, Gardulf et al., 1991).

MMN

Treatment with immunoglobulin G (IgG) is effective for the maintenance of motor function in patients with multifocal motor neuropathy (MMN) (Harbo et al., 2010).

Various trials have shown a beneficial effect of IVIG on muscle strength in MMN and a comparable effect of SCIG (Eftimov et al., 2009, Harbo et al., 2009, Markvardsen and Harbo, 2017, van Schaik et al., 2005). Although a large number of studies have demonstrated that IVIG treatment is well-tolerated, various systemic adverse event (AE)s have been reported: the majority, such as headache, malaise and chills, are transient and relatively mild, but some rare AEs, such as anaphylactic and skin reactions, are serious (van Schaik et al., 2005). Moreover, repeated venous access and administration in hospital or at home, in the presence of a nurse, is a burden for the patient. Subcutaneous immunoglobulin treatment is considered a good alternative as it can be administered by the patient or informal caregiver and produces fewer systemic ARs (Cocito et al., 2014, Markvardsen and Harbo, 2017).

The main disadvantages with conventional SCIG therapy are: 1) the limited volume of fluid that can be delivered subcutaneously, and 2) the low bioavailability (65%-69%) (Berger et al., 2013) of the conventional SCIG therapy. These limitations in turn require more frequent dosing typically to be weekly to several times a week (Markvardsen et al., 2014) and, in the case of large doses, administration at multiple sites to deliver the entire dose (Harbo et al., 2009, Harbo et al., 2010, Markvardsen et al., 2014).

TAK-771 (immunoglobulin infusion [IGI], 10% with rHuPH20) was developed to address the major limitation of conventional SCIG therapy and it significantly enhances SC administration in primary immunodeficiency disease (PID) by offering improved bioavailability (as compared to conventional SCIG therapy) without requiring greater doses than those administered intravenously (IV) (Schiff et al., 2008). In addition, TAK-771 allows the SC administration of standard PID monthly dosing volumes, and the utilization of infusion rates equal to IV administration while preserving the advantages of SC administration (Schiff et al., 2008). These advantages may be particularly relevant to neurology indications, including immune-medicated neuropathies for IgG usage, which require immunomodulatory doses up to five-times higher than immune replacement doses.

4.1.2 Description of Investigational Products

TAK-771 consists of recombinant human hyaluronidase and 10% IGI.

4.1.2.1 Recombinant Human Hyaluronidase (rHuPH20)

rHuPH20 (molecular weight of approximately 61 kDa) is produced from genetically engineered Chinese Hamster Ovary cells containing a deoxyribonucleic acid (DNA) plasmid encoding for a soluble fragment of human hyaluronidase PH20. rHuPH20 is a soluble recombinant form of human hyaluronidase that modifies the permeability of connective tissue through the hydrolysis of hyaluronan. rHuPH20 acts locally and transiently within the SC space to increase the tissue dispersion and absorption of other injected drugs and fluids.

4.1.2.2 Immune Globulin Infusion 10% (Human) (10% IGI)

A 10% IGI is manufactured from human plasma by employing a modified Cohn-Oncley cold alcohol fractionation process, as well as cation and anion exchange chromatography. Screening against potentially infectious agents (such as hepatitis A virus [HAV], hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV], and parvovirus B19 [B19V]) begins with the donor selection process and continues throughout plasma collection and preparation.

4.1.3 Findings from Nonclinical and Clinical Studies

Findings from nonclinical and clinical studies for TAK-771 are detailed in the Investigator's Brochure (IB) for 10% IGI with rHuPH20.

4.2 Rationale for the Proposed Study

Immunoglobulin has been widely used for patients with primary immunodeficiency (PID), CIDP, and MMN. The administration route for IG replacement therapy for PID used to be mostly intravenous, but facilitated subcutaneous injection has been as a major alternative option since TAK-771's approval for PID in US and EU (Wiesik-Szewczyk et al., 2020). Currently, a double-blind, placebo-controlled clinical trial of TAK-771 for patients with CIDP is ongoing in US (NCT02549170). In addition to that, this proposed study will evaluate the efficacy, safety, and tolerability of TAK-771 in Japanese patients with CIDP/MMN. Feasibility of self-administration will be also examined.

4.3 Benefit/Risk Profile

The clinical program for 10% IGI with rHuPh20 includes 7 completed interventional clinical studies in primary immunodeficiency disease (PID) and healthy volunteers, and 1 completed non-interventional registry study in women exposed to treatment before or during pregnancy (pregnancy registry). Together, these studies demonstrate the efficacy, pharmacokinetics, safety and tolerability of 10% IGI with rHuPH20. rHuPH20 increased the bioavailability of 10% IGI administered SC normalized by area under the curve (AUC)/dose/kg body weight (BW) by approximately 20%, thus reducing the clinically effective dose. When administered at 108% of the IV dose, 10% IGI with rHuPH20 was pharmacokinetically equivalent to 10% IGI administered IV with respect to $AUC_{0-\tau}$ and resulted in comparable trough IgG levels. The IgG trough levels determined for all 3 treatment modalities assessed were well above 5.0 g/L, the accepted minimum level for effective prophylaxis against infections in patients with PID (Orange et al., 2006). Further information is provided in the IB for IGI 10% (Human) with rHuPH20 as well as Prescribing Information for TAK-771 and Summary of Product Characteristics (SmPC) for TAK-771.

A 10% IGI with rHuPH20 administered over 3 years at a similar frequency to IVIG was safe with a comparable adverse event (AE) profile to SCIG at infusion volumes and rates equivalent to IVIG, and effectively maintained low rates of infection in patients with PID (Wasserman et al., 2015). Large infusion volumes >600 mL/site were well-tolerated, enabling treatment of pediatric and adult patients with PID at the same interval used for 10% IGI administered IV. When administered at 108% of the IV dose, 10% IGI with rHuPH20 resulted in a somewhat lower rate of infections per subject-year than 10% IGI administered IV or SC. Trough IgG levels were comparable for 10% IGI with rHuPH20 and 10% IGI administered IV.

Protective trough levels were maintained during long-term treatment with 10% IGI with rHuPH20. 10% IGI with rHuPH20 reduced the clinically effective SC dose of 10% IGI compared to SC administration alone and resulted in decreased frequency, severity and duration of local induration. A decline in the rate of related local AEs per subject per year was observed during long-term replacement therapy with 10% IGI with rHuPH20 in subjects with PID.

Across 7 completed clinical studies, 2 serious adverse events (SAEs) were reported that were considered to be related to 10% IGI with rHuPH20. These events were cases of hemolytic anemia in healthy volunteers. They were conservatively assessed by the investigator as possibly being related to 10% IGI with rHuPH20, with an alternative etiology of viral infection (H1N1 influenza A California) which affected 10 of the 12 subjects who participated in this study and was documented by seroconversion. In pregnancy registry (Study 161301), a total of 2 SAEs (thrombocytopenia and pre-eclampsia) were reported in one mother in the 10% IGI with rHuPH20 arm in the prospective cohort. A total of 2 SAEs (cleft lip without cleft palate and talipes calcaneovalugus) were reported in two infants in the 10% IGI with rHuPH20 arm. None of these events was related to treatment with 10% IGI with rHuPH20.

The rate of adverse drug reactions (ADRs) per infusion obtained for 10% IGI with rHuPH20 compares favorably with published data on SCIG (Ochs et al., 2006). A lower rate of systemic ADRs was reported for 10% IGI with rHuPH20 than IVIG treatment; this is in line with numerous studies comparing SCIG with IVIG (Berger, 2004, Gardulf and Hammarström, 1996, Moore and Quinn, 2008).While in Study 160603 local ADRs during 10% IGI with rHuPH20 treatment, which were mostly mild and moderate in severity, were reported at a rate of 0.203 AEs per infusion, the frequency of local ADRs per infusion was as low as 0.103 during long-term treatment with 10% IGI with rHuPH20 in extension Study 160902.

A reduction of ADRs over time was also observed in an integrated analysis of Studies 160603 and 160902 which showed a decline in the rate of related AEs (excluding infections) per subject per year from 5.63 at Months 1 to 12 to <1.55 at Months 24 to 40 of 10% IGI with rHuPH20 treatment.

The nature of ADRs was similar for 10% IGI administered SC in Studies 160601 and 160603, and for 10% IGI with rHuPH20 treatment in Studies 160603, 160902, and 161101; the most commonly reported reactions were infusion site reactions.

Infusion site reactions are expected in most patients during SCIG therapy, but they are not reported to be troublesome in the majority of patients (Gardulf et al., 1995, Misbah et al., 2009, Moore and Quinn, 2008).

Non-neutralizing antibody titers ≥1:160 were observed in 13 subjects in Study 160603. Of these subjects, 11 rolled over into the extension Study 160902. Titers ≥1:160 persisted in 6/11 subjects; however, in a majority of the 11 subjects, rHuPH20-reactive binding antibody titers declined during 10% IGI with rHuPH20 despite continued exposure. After switching to 10% IGI without rHuPH20, antibody titers further decreased during the Safety Follow-up period of Study 160902. Two subjects developed rHuPH20-reactive binding antibody titers ≥1:160 in Study 160902; in both subjects rHuPH20-reactive binding antibody titers of 1:160 were reported once. No subjects in Study 161101 developed binding antibody titers ≥1:160.

Investigations of animal models investigations did not show any cross reactivity of rHuPH20-reactive antibodies with other hyaluronidases. Therefore, the risks of developing circulating rHuPH20-reactive binding antibodies with an impact on hyaluronidase catabolism would have a low probability of occurrence. Additional animal studies concluded that rHuPH20 reactive antibodies are incapable of preventing oocyte fertilization including in non-human primates.

There have been no serious hypersensitivity reactions, including anaphylactic reactions, attributed to rHuPH20 in the studies with 10% IGI with rHuPH20. The current clinical and safety data for 10% IGI with rHuPH20 demonstrate that exposure is safe and well-tolerated, and there has been no evidence of a lack of treatment effect when rHuPH20-reactive binding antibodies have been detected. Based upon data available to date, the incidence of the formation of anti-rHuPH20 antibodies is low, no neutralizing antibodies have been observed, no clinical signs or symptoms have been associated with positive anti-rHuPH20 antibody titers. A risk management plan has been developed to further monitor the potential risk of the formation of rHuPH20-reactive antibodies following the administration of 10% IGI with rHuPH20.

10% IGI with rHuPH20 is contraindicated in individuals with hypersensitivity to hyaluronidase, including rHuPH20, and to IgG, particularly in patients who have developed antibodies against IgA. Although true hypersensitivity reactions are rare, adherence to the recommended infusion rate and monitoring for ADRs throughout the infusion period are advised.

IgG administration may impair the efficacy of live attenuated virus vaccines such as rubella, mumps and varicella for 6 weeks to 3 months, therefore these vaccines should not be administered within 3 months of 10% IGI with rHuPH20. In the case of live attenuated measles vaccine, antibody status should be determined before vaccination.

Antibodies transferred passively by 10% IGI with rHuPH20 treatment may result in transient false positive results in serological tests.

5. STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objectives

To evaluate the efficacy of TAK-771 in Epoch 1 as a maintenance therapy for Japanese patients with stable CIDP and MMN to prevent relapse or progression of motor function.

5.1.2 Secondary Objectives

1. To assess the safety and tolerability of TAK-771 in Epoch 1 and Epoch 2 as a maintenance therapy for Japanese patients with CIDP and MMN.
2. To assess the efficacy of TAK-771 in Epoch 1 and Epoch 2.

5.1.3 Tertiary Objectives

1. To assess the serum trough levels of total IgG.
2. To assess the number of subjects using self-administration.

5.2 Endpoints

5.2.1 Primary Endpoint(s)

Cohort 1 (CIDP)

Occurrence of relapse in Epoch 1 (worsening of functional disability defined as an increase of ≥1 point relative to the pre-SC treatment baseline score in adjusted INCAT disability score).

Cohort 2 (MMN)

Change in maximum grip strength in the more affected hand in Epoch 1 (per baseline measurement point, investigators judge which of both hands is more affected).

5.2.2 Secondary Endpoints

5.2.2.1 Safety

Cohort 1 (CIDP) and Cohort 2 (MMN)

- Treatment-emergent adverse events (TEAEs) and SAEs regardless of causality.
- Causality of related SAEs and/or AEs.
- Serious and/or nonserious ARs plus suspected ARs*.
- Treatment-emergent SAEs and/or AEs associated with infusions, regardless of causality
- Causality of related SAEs and/or AEs associated with infusions

- AEs temporally associated with infusions (defined as AEs occurring during or within 72 hours after completion of an infusion)
- Serious and/or nonserious ARs plus suspected ARs associated with infusions
- Treatment-emergent systemic AEs associated with infusions
- Treatment-emergent local infusion site reactions associated with infusions
- Infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs.
- Development positive titer (≥160) binding antibodies, or develop neutralizing antibodies, to rHuPH20.

* In the current study, an AR/suspected AR is defined as an AE that is considered by the investigator to be related or not related to IP administration, or for which the causality is indeterminate or missing, or that begins during infusion of IP or within 72 hours following the end of IP infusion.

5.2.2.2 Efficacy

Cohort 1 (CIDP)

- CIDP worsening in Epoch 1 (defined as a ≥8 kPa decrease in the hand grip strength in the more affected hand) OR ≥4 points decrease in Rasch-Built Overall Disability Scale (R-ODS) relative to the pre-SC treatment baseline score at 2 consecutive time points (at the time of withdrawal from the SC treatment period).
- Time to relapse in Epoch 1 and Epoch 2.
- Change from pre-SC treatment baseline in R-ODS score in Epoch 1.
- Change from baseline in an average of handgrip strength of both hands in Epoch 1.

Cohort 2 (MMN)

- Medical Research Council (MRC) sum score in Epoch 1.
- Guy's Neurological Disability Scale (GNDS) in upper limb and lower limb categories in Epoch 1.
- Change from baseline in an average of handgrip strength of both hands in Epoch 1.

5.2.3 Tertiary Endpoints

- Serum trough levels of total IgG.
- Number of subjects received the study drug through self-administration.

6. STUDY DESIGN AND DESCRIPTION

6.1 Study Design

This is a Phase 3, prospective, multicenter, open-label, non-controlled, single-arm study. There are two treatment Epochs, with 2 cohorts of CIDP and MMN patients in this study. A schematic of the study design is shown in Figure 6-1. Investigational product administration and site visit schedule are the same in Cohort 1 and Cohort 2, but primary endpoint measurements differ.

This study will enroll subjects with a confirmed diagnosis of CIDP or MMN, who have remained on a stable dosing regimen (monthly equivalent dose of 0.4 to 2.4 g/kg BW with a dosing interval of 2 to 6 weeks) of IVIG therapy for at least 12 weeks prior to screening.

After informed consent is obtained, subjects will undergo screening and baseline procedures for the determination of eligibility and will continue to receive their own IVIG treatment at the same dose and dosing intervals prescribed prior to their entry into this study. No dosing adjustment of IVIG treatment is allowed except in cases of intolerability.

Eligible subjects will receive TAK-771 SC for a treatment period of 6 months in Epoch 1. The IgG dose of TAK-771 per month will be adjusted to be equivalent to subject's monthly IVIG dose. The number of infusion visits and site visits during the SC treatment period will vary across subjects depending on whether their infusion cycles are every 2, 3, or 4 weeks. If a subject with CIDP has met relapse criteria or a subject with MMN has been judged as being worsened by the investigator, the subject will be discontinued from the study treatment (See details in Section 7.4). For safety and tolerability data, the sponsor set the minimum duration of Epoch 2 as 6 months. After the first 6 months of Epoch 2, if the subject is tolerating the drug well and voluntarily wishes to continue TAK-771 treatment, the subject can stay in the study until the commercial TAK-771 is available in each study site. After the first 6 months of Epoch 2, the investigator may adjust the dose of TAK-771 administration in every 3 months based on the process shown below. Schedule of assessments is varied across the dosing interval (See the details in Appendix A).

6.1.1 TAK-771 Dose and Dosing Interval in Epoch 1

This study employs a dose ramp-up schedule until the subject's full-dose is reached in order to increase the SC infusion volume gradually. Dosing during ramp-up period for tolerated doses are shown in Table 6-1, Table 6-2, and Table 6-3 for 2-week, 3-week, and 4-week dosing interval regimen, respectively. After the ramp-up period, full-dose administration with regular intervals will be continued in Epoch 1 if it is tolerable.

Table 6-1. Subjects with 2-week Dosing Interval Regimen with TAK-771

Week	Infusion Number	Dose of 10% IGI
Week 1	1st. infusion	1/2 of full dose
Week 2	2nd. infusion	1/2 of full dose
Week 3 and the following 2-week intervals	3rd infusion	full dose

Table 6-2. Subjects with 3-week Dosing Interval Regimen with TAK-771

Week	Infusion Number	Dose of 10% IGI
Week 1	1st. infusion	1/3 of full dose
Week 2	2nd. infusion	1/3 of full dose
Week 3	3rd infusion	2/3 of full dose
Week 5 and the following 3-week intervals	4th infusion and the following infusions	full dose

Table 6-3. Subjects with 4-week Dosing Interval Regimen with TAK-771

Week	Infusion Number	Dose of 10% IGI
Week 1	1st. infusion	1/4 of full dose
Week 2	2nd. infusion	1/4 of full dose
Week 3	3rd. infusion	1/2 of full dose
Week 5	4th infusion	3/4 of full dose
Week 8 and the following 4-week intervals	5th infusion and the following infusions	full dose

6.1.2 TAK-771 Dose and Dosing Interval in Epoch 2

The dose and dosing interval of TAK-771 in the first 6 months of Epoch 2 are fixed as same as those in Epoch 1. At the end of the first 6 months of Epoch 2, the dosing interval of TAK-771 can be changed once considering subject's burden and preference (Step 1). The dose of TAK-771 may be adjusted at the discretion of the investigator in every 3 months, as medically necessary and/or as tolerated by the subject* (Step 2).

Step 1. To determine the dosing interval of TAK-771

The investigator can choose the dosing interval of TAK-771 from the following 3 options; every 2 weeks, every 3 weeks, every 4 weeks. Basically, the interval should be fixed after that, only except if medically necessary**.

Step 2. To determine the dose of TAK-771

The investigator can adjust (decrease, keep, or increase) the dose of TAK-771 in every 3 months. By the end of the preceding 3 months, the investigator needs to determine the dose per each administration for the next 3 months under the following 3 limitations.

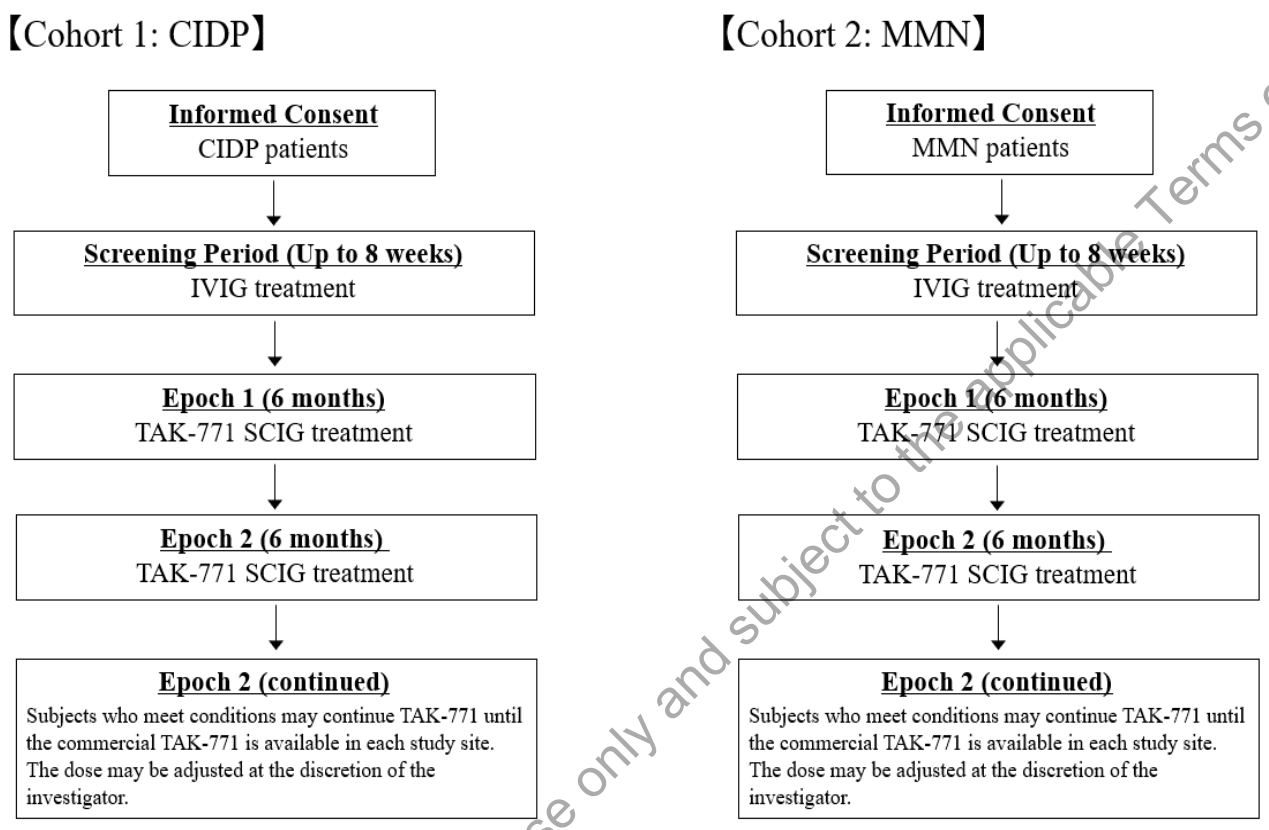
1. The maximum dose of IgG (calculated as cumulative monthly dose regardless of dosing interval) is equivalent to 2.4 g/kg BW.
2. Variations in dose adjustment should be up to ±15% of the dose in the preceding 3 months.
3. To change the dose of TAK-771 in the middle of the planned 3 months is not allowed, except if medically necessary**.

Notes:

*The subjects have to receive investigator's assessment at least once in 3 months (see the schedule of Epoch 2).

**If subject's symptoms worsened, the investigator can determine to change the treatment (ie. to start the excluded medication listed in Section 7.3) at any timing in the middle of the planned 3 months in Epoch 2. In that case, the subject will have to undergo early termination visit and discontinue the Epoch 2.

Figure 6-1. Schematic of Study Design



CIDP = chronic inflammatory demyelinating polyradiculoneuropathy; IVIG = intravenous immunoglobulin; MMN = multifocal motor neuropathy; SCIG = subcutaneous immunoglobulin.

6.2 Justification for Study Design, Dose, and Endpoints

This study will provide evidence for efficacy, safety and tolerability of TAK-771 in Japanese patients with CIDP and MMN. Since the number of eligible subjects is small because of prevalence, an open-label non-controlled single-arm design was chosen.

The IgG dosing regimen for TAK-771 will be equivalent to that for previous treatment of each subject when administered at a dosing interval of every 2, 3, or 4 weeks. The efficacy and the safety of IVIG maintenance therapy for CIDP had been demonstrated in global study and JPN local study with the same dose administration and the same dosing interval. There is no ethnic difference regarding dose.

In the pivotal PID Phase 3 study (Protocol 160603), the geometric mean area under the concentration-time curve over a dosing interval ($AUC_{0-\tau}$) ratio (SC/IV) for IgG was found to be 93.3%, with a 90% confidence interval (CI) of 91.4% to 95.2%. The median $AUC_{0-\tau}$ (normalized to a 1-week dosing interval) was similar after SC versus IV administration (90.5 vs 93.9 g × days/L). As expected with SC administration, the median peak concentration (C_{max}) was lower after SC than after IV infusion (15.5 g/L vs 21.9 g/L) while the median time to reach C_{max} was longer (T_{max}: 5.0 vs 0.1 days). Clearance (or apparent clearance for SC administration) and trough concentration (C_{min}) after SC infusion were similar to the values calculated after IV infusion. The median ratio of IgG trough levels for TAK-771 was 98.5% (95% CI: 93.4%; 102.5%).

TAK-771 infusions were given at an adjusted dose of 108% of IV dose to provide equivalent area under the IgG concentration-time curve (AUC) at steady state. This illustrates (a) the expected difference in C_{max} and T_{max} for the two modes of administration, (b) the superimposition of IgG concentration-time curves during the elimination phase following SC and IV administration, and (c) comparable trough IgG levels after SC and IV administration. For this reason, no dose conversion factor will be applied; that is, subjects entering the study will receive the same IgG monthly equivalent dose as their own pre-study IVIG treatment regimen that was effective in maintaining the subject's CIDP condition and MMN conditions.

Additionally, from a viewpoint of medical science, the dose and the interval of IgG needs to be optimized. Clinical guideline for CIDP published by Japanese Society of Neurology recommends to optimize the maintenance dose of IVIG and its administration intervals in each individual case (Japanese Society of Neurology). It is difficult to predict the long-term prognosis, but a few of CIDP cases can achieve complete remission (Kuwabara et al., 2006). The efficacy of IVIG on MMN should be carefully assessed in long-term observation because it would be attenuated possibly due to axonal degeneration (Terenghi et al., 2004). Based on these evidences, in the current study, the sponsor provides some flexibility on the dose in Epoch 2.

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for the TAK-771, such that the risk is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor, an Institutional Review Board (IRB) or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7. SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to entry into the study:

1. Be a Japanese person.
2. The subject is male or female ≥18 years old at the time of screening.
3. Subject has a documented diagnosis of definite or probable CIDP (focal atypical CIDP and pure sensory atypical CIDP will be excluded) or definite or probable MMN, as confirmed by a neurologist specializing/experienced in neuromuscular diseases to be consistent with the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria.
4. Subject has responded to IgG treatment in the past (partial or complete resolution of neurological symptoms and deficits), and must currently be on stable doses of IVIG treatment within the dose range equivalent to a cumulative monthly dose of 0.4 to 2.4 g/kg BW (inclusive) administered intravenously for at least 12 weeks prior to screening. The dosing interval of IVIG treatment must be between 2 and 6 weeks (inclusive). Variations in the dosing interval of up to ±7 days or monthly dose amount of up to ±20% between subject's pre-study IgG infusions are within acceptable limits.
5. CIDP subjects only - INCAT disability score between 0 and 7 (inclusive). Subjects with INCAT scores of 0, 1 (whether from upper or lower extremities), or 2 (if at least 1 point is from an upper extremity) at screening and/or baseline will be required to have a history of significant disability as defined by an INCAT disability score of 2 (must be exclusively from the lower extremities) or greater documented in the medical record. Subjects will be eligible if one of the below eligibility criteria are met:
    a. Screening and Baseline INCAT disability score between 3 and 7 inclusive.
    b. Screening and/or Baseline INCAT disability score of 2 (both points are from lower extremities)
    c. Screening and/or Baseline INCAT disability score of 2 (both points are not from lower extremities) AND has at least a score of 2 or greater documented in the medical record prior to screening. If a score was greater than 2 documented in the medical record prior to screening at least 2 points must be from lower extremities.
    d. Screening and/or Baseline INCAT disability score of 0 or 1 AND has at least a score of 2 or greater (both from lower extremities) documented in the medical record prior to screening, at least 2 points must be from lower extremities.

6. If female of childbearing potential, the subject must have a negative pregnancy test at screening and agree to employ a highly effective contraceptive measure throughout the course of the study and for at least 30 days after the last administration of IP.
7. The subject is willing and able to sign an Informed Consent Form (ICF).
8. The subject is willing and able to comply with the requirements of the protocol.

7.2 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

CIDP patients

1. Subjects with focal atypical CIDP or pure sensory atypical CIDP or multifocal acquired demyelinating sensory and motor neuropathy (MADASAM).
2. Subjects with any neuropathy of other causes, including:
    a. Hereditary demyelinating neuropathies, such as hereditary sensory and motor neuropathy (HSMN) (Charcot-Marie-Tooth [CMT] disease), and hereditary sensory and autonomic neuropathies (HSANs).
    b. Neuropathies secondary to infections, disorders, or systemic diseases such as Borrelia burgdorferi infection (Lyme disease), diphtheria, systemic lupus erythematosus, POEMS (polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes) syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, lymphoma, and amyloidosis.
    c. Multifocal motor neuropathy (MMN).
    d. Drug-, biologic-, chemotherapy-, or toxin-induced peripheral neuropathy.

MMN patients

3. Subject with other neuropathies (eg, diabetic, lead, porphyric or vasculitic neuropathy, chronic inflammatory demyelinating polyradiculoneuropathy, Lyme neuroborreliosis, post radiation neuropathy, hereditary neuropathy with liability to pressure palsies, CMT neuropathies, meningeal carcinomatosis).

CIDP/MMN Patients

4. Subject with immunoglobulin M (IgM) paraproteinemia, including IgM monoclonal gammopathy with high titer antibodies to myelin-associated glycoprotein.
5. Subject with presence of prominent sphincter disturbance.

6. Subject with any central demyelinating disorders such as multiple sclerosis.
7. Subject with any chronic or debilitating disease, or central nervous disorder that causes neurological symptoms or may interfere with assessment of endpoint measures, including (but not limited to) arthritis, stroke, Parkinson's disease, and diabetic peripheral neuropathy.

   (Subjects with clinically diagnosed diabetes mellitus who do not have diabetic peripheral neuropathy and who have adequate glycemic control with hemoglobin A1c [HbA1c] level of <7.5% at screening will be eligible for the study, provided the electrodiagnostic criteria are consistent with the diagnosis of a definite or probable CIDP consistent with the EFNS/PNS 2010 criteria and the subject agrees to maintain adequate glycemic control.)
8. Subject with congestive heart failure (New York Heart Association [NYHA] class III/IV), unstable angina, unstable cardiac arrhythmias, or uncontrolled hypertension (defined as diastolic blood pressure >100 mmHg and/or systolic blood pressure >160 mmHg).
9. Subject with a history of deep vein thrombosis or thromboembolic events (eg, cerebrovascular accident, pulmonary embolism) within 12 months prior to screening.
10. Subject with condition(s) which could alter protein catabolism and/or IgG utilization (eg, protein-losing enteropathies, nephrotic syndrome).
11. Subject with a known history of chronic kidney disease, or glomerular filtration rate of <60 mL/min/1.73m^2 estimated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at the time of screening.
12. Subject with active malignancy requiring chemotherapy and/or radiotherapy, or history of malignancy with less than 2 years of complete remission prior to screening. Exceptions to this exclusion are: adequately treated basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, and stable prostate cancer not requiring treatment.
13. Subject with clinically significant anemia that precludes repeated blood sampling during the study, or hemoglobin (Hgb) level of <10.0 g/dL at the time of screening.
14. Subject with a known history of hypersensitivity or ARs such as urticaria, breathing difficulty, severe hypotension, or anaphylaxis following administration of human blood products such as human IgG, albumin, or other blood components.
    Note: Clinically non-significant skin reactions, as per the investigator's and the sponsor medical monitor's discretion, do not meet this exclusion criterion. Clinically non-significant skin reactions may include local reactions to injection such as injection site's itching, redness, erythema, or swelling.

15. Subject has a known allergy to hyaluronidase of human (including recombinant human hyaluronidase) or animal origin such as bee or wasp venom.
16. Subject with immunoglobulin A (IgA) deficiency and antibodies against IgA and a history of hypersensitivity.
17. Subject with an abnormal laboratory values at screening meeting any one of the following criteria:
    a. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) >2.5 x upper limit of normal (ULN).
    b. Platelet count <100,000 cells/µL.
    c. Absolute neutrophil count (ANC) <1000 cells/µL.
18. Subject has a known history of or is positive at screening for one or more of the following: hepatitis B surface antigen (HBsAG), polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for human immunodeficiency virus (HIV) Type 1/2.
19. Subject has received or is currently receiving treatment with immunomodulatory/immunosuppressive agents within 6 months prior to screening.
20. Subject has received or is currently receiving treatment with any corticosteroids dose within 8 weeks prior to screening, regardless of indication.
21. Subject has undergone PE within 3 months prior to screening.
22. Subject has any disorder or condition that in the investigator's judgment may impede the subject's participation in the study, pose increased risk to the subject, or confound the results of the study.
23. Subject is nursing or intends to begin nursing during the course of the study.
24. Subject has participated in another clinical study involving an IP or investigational device within 30 days prior to enrollment, or is scheduled to participate in another clinical study involving an IP or investigational device during the course of this study.
25. Subject is a family member or employee of the investigator.
26. Subjects with known acquired or inherited thrombophilic disorders. These will include the specific types of acquired or inherited thrombophilic disorders that could put subjects at risk of developing thrombotic events. Examples include
    a. Hereditary thrombophilia:
        i. Factor V Leiden mutation.
        ii. Prothrombin 20210A mutation.

iii. Protein C deficiency.

iv. Protein S deficiency.

v. Anti-thrombin deficiency.

b. Acquired thrombophilia:

i. Anti-phospholipid antibody syndrome.

ii. Activated protein C Resistance acquired.

iii. Homocystinemia.

7.3 Excluded Medications and Non-drug Therapies

The following medications and non-drug therapies are not permitted during the course of the study:

- Corticosteroids, regardless of indication.
  - Non-systemic corticosteroids (eg, topical, ophthalmic, or inhaled glucocorticoids) are allowed at any time before screening and during the course of the study.
- Immunomodulatory/immunosuppressive agents.
- Plasma exchange
- Other IgG products, with the exception of the subject's IVIG treatment during the screening period.
- Hyperimmune serum.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or IP should be recorded in the electronic case report form (eCRF) using the following categories. The criterion #8 is applied only for subjects who completed Epoch 1 and the first 6 months of Epoch 2. While relapse of CIDP is defined depending on INCAT scores, worsening of MMN is judged based on investigator's comprehensive assessment. For screen failure subjects, refer to Section 9.1.15.

1. Pretreatment event (PTE) or AE. The subject has experienced a PTE or AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the PTE or AE.

2. Significant protocol deviation. The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued participation poses an unacceptable risk to the subject's health.
3. Lost to follow-up. The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
4. Voluntary withdrawal. The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (ie, withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category).
5. Study termination. The sponsor, IRB, or regulatory agency terminates the study.
6. Pregnancy. The subject is found to be pregnant.

   Note: If the subject is found to be pregnant, the subject must be withdrawn immediately. The procedure is described in Section 9.1.11.
7. For CIDP subjects: The subjects who meet any one of the following criteria (a to c) will be discontinued.

   For MMN subjects: The subjects who meet any one of the following criteria (b or c) will be discontinued.

   a. CIDP relapse (worsening of functional disability defined as an increase of ≥1 point relative to the pre-SC treatment baseline score in adjusted INCAT disability score)
   b. If the investigator has determined to start the excluded medications or non-drug therapies described in Section 7.3.
   c. If the investigator has determined that the subject is not benefiting from study treatment for any other reason regarding the lack of efficacy.
8. If the investigator has determined to terminate TAK-771 administration in Epoch 2 (after the first 6 months) based on investigator's careful observation that the subject may be in remission.
9. Other.

   Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study discontinuation or withdrawal criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator. In addition, efforts should be made to perform all procedures scheduled for the early termination Visit. Discontinued or withdrawn subjects will not be replaced.

8. CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

8.1.1.1 Study Drug

The study drug is TAK-771 (IGI 10% and rHuPH20).

rHuPH20

rHuPH20 drug product is supplied as a sterile, clear, colorless, ready-for-use solution in the label strength of 160 U/mL, containing the additional excipients sodium chloride, sodium phosphate, human albumin, ethylenediaminetetraacetic acid disodium, calcium chloride, and sodium hydroxide and/or hydrochloric acid added for pH adjustment. rHuPH20 solution contains 0.1% human albumin with an approximate pH of 7.4 and osmolality of 290 to 350 mOsm. rHuPH20 solution is preservative-free. rHuPH20 solution provides for high margins of safety with respect to viruses, due to comprehensive virus testing at the Master Cell Bank, Working Cell Bank and bulk harvest stage, effective virus reduction during the purification process, and the use of pharmaceutical grade human albumin as an excipient with no other materials of human or animal origin involved in the manufacturing process.

Dosage Form: Injection, solution

Packaging: rHuPH20 drug product (160 U/mL) will be supplied as a clear, colorless, ready-for-use sterile liquid preparation in single-use glass vials. The product should be inspected visually for particulate matter and discoloration. The product should not be used if particulate matter and/or discoloration is observed.

Labeling: The product will be labeled according to the regulatory requirements for clinical studies.

IGI 10%

10% IGI is manufactured from human plasma by employing a modified Cohn-Oncley cold alcohol fractionation process, as well as cation and anion exchange chromatography. Screening against potentially infectious agents (such as HAV, HBV, HCV, HIV, and B19V) begins with the donor selection process and continues throughout plasma collection and preparation. To further improve the margin of safety, three validated, dedicated, independent, and effective virus inactivation/removal steps have been integrated into the manufacturing and formulation processes, namely solvent/detergent treatment, nanofiltration, and incubation at a low pH and elevated temperature in the final formulation.

The finished medicinal product, 10% IGI, is a purified, functionally intact IgG solution formulated with 0.25 M glycine (for a stabilizing effect) at 10% w/v protein concentration and a pH of 4.6 to 5.1.

The preparation is an isotonic solution containing approximately 100 mg of protein per mL, of which at least 98% is IgG with an IgG subclass distribution representative of native human plasma. The product contains no preservatives.

Dosage Form: Injection, solution.

Packaging: 10% IGI will be supplied as a ready-for-use sterile liquid preparation in single-use glass vials. 10% IGI is a clear or slightly opalescent and colorless or pale yellow solution. The product should be inspected visually for particulate matter and discoloration. The product should not be used if particulate matter and/or discoloration is observed.

Labeling: 10% IGI will be labeled according to regulatory requirements for clinical studies.

8.1.1.2 Sponsor-Supplied Drug

Sponsor-supplied drugs referenced in other sections of the protocol include the study drug TAK-771 (rHuPH20 and IGI 10%).

8.1.1.3 IVIG 10% (Non-Investigational Product)

The IVIG product administered during screening is an approved IV immunoglobulin procured locally, which is administered as per local product label. Additional information is provided in the appropriate product package label. IVIG will not be managed by interactive response technology (IRT) and will not be provided by the sponsor as IP.

The IVIG used in screening will be the same IVIG preparation being administered to the patient prior to enrollment in the study and will be sourced by the sites. The lot number of IVIG used for the study should be recorded in eCRF by clinical site personnel.

8.1.2 Storage

TAK-771 must be stored under refrigerated conditions (2° to 8°C). Do not freeze the product. Do not use if expiration date is exceeded.

The Investigator has overall responsibility for ensuring that study drug is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented. Study drug is distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the labels as they are distributed.

The sponsor should be notified immediately if there are any changes to the storage area of the study drug that could affect the integrity of the products, eg, fumigation of a storage room. Study drug must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. Study drug must be stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

8.1.3 Dose and Regimen

Investigational product administration methods are the same for CIDP subjects and MMN subjects. Subcutaneous infusion of rHuPH20 solution at a dose of 80 U/g IgG will be administered first, followed by SC infusion of 10% IGI within 10 minutes of completion of the infusion of rHuPH20 solution. The first SC administration will take place 2 weeks (±3 days) following the subject's last IVIG administration at screening. To gradually increase the SC infusion volume, a dose ramp-up schedule will be employed until the subject's full dose is reached. The recommended sites for the infusion of TAK-771 are the middle to upper abdomen and thighs.

rHuPH20 and 10% IGI solutions for administration must be prepared according to separate written procedures which will be provided in infusion manuals.

rHuPH20

Dose: 80 U/g IgG (rHuPH20 drug product: 160 U/mL)

Dosing interval: Same as 10% IGI

Mode of Administration: For the initial 2 administrations, infuse rHuPH20 solution at 60 to 120 mL/h/site as tolerated (or a total of 120 to 240 mL/h, or 180 to 360 mL/h over 2 and 3 sites, respectively). For subsequent administrations, rHuPH20 solution infusion rate may be increased as tolerated by the subject and at the discretion of the investigator, but not to exceed 300 mL/h/site (or not to exceed a total of 600 mL/h or 900 mL/h over 2 and 3 sites, respectively).

IGI 10%

Dose: In Epoch 1 and the first 6 months of Epoch 2, the total amount of IgG administered per month will be maintained as equivalent to that of previous IVIG treatment (a cumulative monthly dose of 0.4 to 2.4 g/kg BW). After the first 6 months of Epoch 2, it may be adjusted at the discretion of the investigator in every 3 months, as medically necessary and/or as tolerated by the subject.

Dosing interval: In Epoch 1 and the first 6 months of Epoch 2, each subject's dosing interval should be kept as the same interval (every 2, 3, or 4 weeks, except during the ramp-up period) as determined prior to the first infusion of study drug based on previous IVIG treatment. Adjustment to dosing interval is not allowed, except due to intolerability. After the first 6 months of Epoch 2, it can be changed once.

Mode of Administration: SC infusion, to be administered via an infusion pump (Sapphire™ Multi-Therapy, see Section 8.2) at 1, 2, or 3 infusion sites per infusion day.

Maximum infusion rate

For the initial 2 infusions, the maximum infusion rate should be 80 mL/h and 240 mL/h per site, for subjects <40 kg and ≥40 kg BW, respectively.

Step-wise increases are suggested in subsequent infusions with rate increases of up to 300 mL/h per infusion site (or up to a total of 600 mL/h over 2 sites if bifurcated needle set is used, or up to a total of 900 mL/h if trifurcated needle set is used) for subjects weighing ≥40 kg. For subjects weighing <40 kg, infusion rates of up to 160 mL/h per infusion site (or up to a total of 320 and 480 mL/h over 2 and 3 sites if bifurcated and trifurcated needle set is used, respectively).

Volume of infusion per site

10% IGI solution may be administered at a volume of up to 600 mL per infusion site for subjects ≥40 kg or up to 300 mL per infusion site for subjects <40 kg, as tolerated. On a given infusion day, the maximum infusion volume should not exceed 1200 mL for subjects weighing ≥40 kg or 600 mL for subjects weighing <40 kg.

If a subject's total IgG dose on a given day exceeds 1200 mL for subjects weighing ≥40 kg or 600 mL for subjects weighing <40 kg, or exceeds the SC maximum infusion volume the subject can tolerate, the TAK-771 dose may be administered over multiple days as divided doses with 48 to 72 hours between doses (eg, Day 1 and Day 3 of a given infusion cycle) to allow absorption of infusion fluid at infusion site(s).

Location of the infusion

Initial SC infusions (during the ramp-up period and, at a minimum, the first full dose infusion) will be administered at the study site, and to provide training to the subject (and/or, as applicable, a caregiver who may assist the subject with self-administration) on self-infusion procedures. At the investigator's discretion, the remainder of the SC infusions may take place at the study site, at the subject's home or other suitable location.

8.1.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol.

All cases of overdose (with or without associated AEs) will be documented on an Overdose page of the eCRF, in order to capture this important safety information consistently in the database. Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s) according to Section 10.

Serious adverse events associated with overdose should be reported according to the procedure outlined in Section 10.2.2.

In the event of drug overdose, the subject should be treated symptomatically.

8.2 Devices Used in Clinical Trial

In this study, 'Device Used in Clinical Trial' is defined as below:

Device name	Sapphire™ Multi-Therapy
Type	Infusion pump
Manufacturer	Q Core Medical Ltd.

8.2.1 Marketing approval

Sapphire Multi-Therapy has not yet been approved for marketing in Japan.

Administration of TAK-771 using Sapphire Multi-Therapy has already been evaluated for the compatibility with the drug and the mechanical suitability by the sponsor in Europe and the US where TAK-771 had been approved and marketed.

8.2.2 Indications for Use in the Study

Sapphire Multi-Therapy is used for SC administration of TAK-771. The device will be used to adjust the administration rate and dose of TAK-771 for SC infusion.

8.2.3 Usage Instructions, Warnings, and Safety Information

For the usage instructions and warnings of Sapphire Multi-Therapy, see the User Manual (Q Core Medical Ltd. 2021) that will be provided to investigators. The User Manual includes the latest information about scientific findings.

8.3 Study Drug Assignment and Dispensing Procedures

An IRT vendor will be used for this study to manage packaged IP supply, IP shipments, receipt of IP at clinical sites, expiry tracking, IP returns, and IP accountability.

Subjects will receive treatment according to the study schedule (see the details in Appendix A). The Enrollment Number will be entered onto the eCRF.

This is an open-label study. Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a study), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The subject number represents a unique number corresponding to study drug allocated to the subject, once eligibility has been determined.

Individual subject treatment is automatically assigned by the IRT. Subjects will be assigned to receive the next available medication ID number allocated to each study site. The medication ID number will be entered onto the eCRF.

8.4 Accountability and Destruction of Sponsor-Supplied Drugs

Drug supplies will be counted and reconciled at the site before being returned to the sponsor or designee.

The investigator or designee must ensure that the sponsor-supplied drug is used in accordance with the protocol and is dispensed only to subjects enrolled in the study. To document appropriate use of sponsor-supplied drug, the investigator or designee must maintain records of all sponsor-supplied drug delivery to the site, site inventory, dispensation and use by each subject, and return to the sponsor or designee.

If permitted by country or local regulations and IRBs, the study drug can be shipped from the site to the subject's home address. Subjects must be provided with instructions on how to receive, store, and ultimately return study/sponsor-supplied drug.

Upon receipt of sponsor-supplied drug, the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, and the medication is in good condition. If quantity and conditions are acceptable, investigator or designee should acknowledge the receipt of the shipment by signing bottom half of the packing list and faxing per instructions provided on the form/by recording in IRT. If there are any discrepancies between the packing list versus the actual product received, Takeda must be contacted to resolve the issue. The packing list should be filed in the investigator's essential document file.

The investigator or designee must maintain 100% accountability for all sponsor-supplied drugs received and dispensed during his or her entire participation in the study. Proper drug accountability includes, but is not limited to:

- Continuously monitoring expiration dates if expiry date/retest date is provided to the investigator or designee.
- Frequently verifying that actual inventory matches documented inventory.
- Verifying that the log is completed for the drug lot/medication ID/job number used to prepare each dose.
- Verifying that all containers used are documented accurately on the log.
- Verifying that required fields are completed accurately and legibly.

If any dispensing errors or discrepancies are discovered, the sponsor must be notified immediately.

The IRT will include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

The investigator or designee must record the current inventory of all sponsor-supplied drugs on a sponsor-approved drug accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied drugs, expiry and/or retest date, date and amount dispensed including initials, seal, or signature of the person dispensing the drug, and the date and amount returned to the site by the subject, including the initials, seal, or signature of the person receiving the sponsor-supplied drug. The log should include all required information as a separate entry for each subject to whom sponsor-supplied drug is dispensed.

All study drug not returned to the site by a subject must be investigated by the site and appropriately documented on the drug accountability log.

Prior to site closure or at appropriate intervals, a representative from the sponsor or its designee will perform sponsor-supplied drug accountability and reconciliation before sponsor-supplied drugs are returned to the sponsor or its designee for destruction. The investigator or designee will retain a copy of the documentation regarding sponsor-supplied drug accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

The investigator will be notified of any expiry date or retest date extension of sponsor-supplied drug during the study conduct. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired sponsor-supplied drug for return to the sponsor or its designee for destruction.

In the event of expiry date extension of sponsor-supplied drug already at the study site, sponsor-supplied drugs may be relabeled with the new expiry date at that site. In such cases, Takeda or its designee will prepare additional labels, certificates of analyses, and all necessary documentation for completion of the procedure at the sites.

The on-site pharmacist (site designee) will receive the pharmacy manual created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied drug. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied drug, and collection of unused medications from the subject as well as return of them to the sponsor or destruction of them.

8.5 Product Quality Complaints

The product quality complaints (including device-used-in-clinical-trial quality issues) should be reported by the investigator to the sponsor [redacted] using the "clinical trial material complaint form" within 24 hours/ 1 business day of the occurrence of product quality complaints, along with any relevant information.

9. STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures and Assessments is located in Appendix A.

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study, and before any protocol-directed procedures are performed according to applicable national and local regulatory requirements and International Council for Harmonisation Good Clinical Practice (ICH GCP). Before use, the ICF will be reviewed by the sponsor and approved by the ethics committee (EC) and regulatory authority, where applicable.

A unique subject identification number (subject number) will be assigned to each subject at the time that informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, race as described by the subject, height, weight, and smoking status of the subject at screening.

Medical history related to CIDP or MMN (such as time of first symptoms and date of diagnosis whichever probable or definite, as available), as well as medication history (eg, use of steroid and/or immunomodulatory/immunosuppressive agents) and/or non-drug therapies (eg, PE) related to the treatment of CIDP or MMN from 6 months (or 3 months for PE) prior to screening throughout the study, will be recorded on the appropriate page of eCRF. Ongoing conditions are considered as concurrent medical conditions (see Section 9.1.8). The subject's medical history within 12 months prior to screening will be described for the following body systems or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

9.1.3 Physical Examination Procedure

At screening and subsequent study visits, a physical examination will be performed on the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes. At screening, if an abnormal condition is detected, the condition will be described on the medical history page of eCRF.

All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

9.1.4 Height, Weight, and BMI

Body height (cm) and weight (kg), as well as BMI will be collected at screening. Subsequently, BW will be re-measured during each treatment period (see Appendix A for detailed measurement timepoints). All BW measurements are to be taken at the study site using the same scale/instrument throughout the study for that individual subject. Subject's self-reported weight will not be used at any time during the course of the study.

9.1.5 Vital Signs Procedure

Vital signs will include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and resting systolic and diastolic blood pressure (mmHg). Blood pressure will be measured when subjects are in the supine/sitting position. Vital signs will be measured at screening (baseline visit), periodically throughout each treatment period, and at study completion/ET visit (See Appendix A for detailed measurement timepoints).

For the initial 3 SC infusions, vital signs are to be monitored and recorded at any time prior to infusion, in the event of occurrence of AE(s), and within 60 minutes of completion of an infusion. During subsequent infusion visits, vital signs will be taken only once during administration, if no AE occur. If AE occurred, vital signs will be taken at the onset of AE (or as soon as the AE is reported) and within 60 minutes of completion of an infusion. Additional vital signs may be taken as deemed medically necessary to monitor the AE. Subjects/caregivers will be instructed that if a healthcare professional is not present at an infusion and the subject experiences an AE necessitating stopping of the infusion, the subject/caregiver should immediately contact the investigator or go to the emergency room/department.

Vital sign values are to be recorded on the appropriate eCRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 10) and record the medical diagnosis (preferably), symptom, or sign on the AE eCRF. Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

9.1.6 Efficacy Measurement

9.1.6.1 Primary Efficacy Measurements

9.1.6.1.1 The Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Scale

The INCAT 10-points disability scale (Hughes et al., 2001) is the most widely used assessment tool to measure the functional activity level of patients with CIDP. The INCAT disability scale consists of upper and lower extremity components, with a maximum of 5 points for the upper extremities (arm disability) and a maximum of 5 points for the lower extremities (leg disability), which are summed for an overall INCAT disability score ranging from 0 to 10 points, where 0 is normal (eg, no upper limb problems and walking not affected) and 10 is severely incapacitated (eg, inability to move either arm for any purposeful movement and restricted to wheelchair, unable to stand and walk a few steps with help). The INCAT disability score is considered to be an effective and responsive tool to assess clinical response to treatment in CIDP (Hughes et al., 2008, Kuwabara et al., 2017, Merkies et al., 2010). An adjusted INCAT disability score is the same as the INCAT disability score, with the only exception in the exclusion of changes from 0 (normal) to 1 (minor symptoms) (or vice versa) in upper limb function since this reflects only a symptomatic change and is not considered to be clinically meaningful change of functional ability (Hughes et al., 2008). A ≥1-point change in the adjusted INCAT disability score is considered to be a clinically significant response to treatment, and has been used as the primary efficacy endpoint in a number of clinical trials in CIDP, including the pivotal trials for other IVIG products (Hughes et al., 2008, Léger et al., 2013).

The adjusted INCAT disability score will be administered at the study site by the investigator/designee using a validated translated version, as applicable. It is recommended that the investigator/designee complete the assessment using the same translated version throughout the course of their participation in the study. If there is ≥1-point increase in the adjusted INCAT score, the investigator will make the subject's discontinuation based on the judgement of relapse.

Further details for INCAT assessments will be provided as a separate document. For detailed administration timepoints, see Appendix A Schedule of Study Procedures and Assessments.

9.1.6.1.2 Hand Grip Strength

Grip strength, a measure of a subject's distal strength and upper limb function, is commonly used in clinical practice to monitor the subject's clinical and functional status, as well as response to treatment (Merkies et al., 2000). In this study, hand grip strength will be administered at the study site by the investigator/designee, using the Martin vigorimeter.

Further details for assessments will be provided as a separate document. For detailed administration timepoints, see Appendix A Schedule of Study Procedures and Assessments.

9.1.6.2 Secondary Efficacy Measurements

9.1.6.2.1 Rasch-Built Overall Disability Scale

The R-ODS is a patient self-reported, linearly-weighted overall disability scale that was specifically designed to capture activity and social participation limitations in patients with immune-mediated peripheral neuropathies including CIDP (van Nes et al., 2011).

The R-ODS is comprised of 24 items for which subjects are asked to rate their functioning (ie, no difficulty, some difficulty, or could not do) related to a variety of everyday tasks at the moment of completion. The R-ODS has a high internal/external validity, acceptable reliability scores, and high discriminant validity. In a recent publication, the R-ODS was reported to be a more responsive scale in capturing clinically meaningful changes over time in newly diagnosed or relapsing patients with Guillain Barré Syndrome, CIDP, and MMN, compared with the widely used ordinal-based INCAT (Draak et al., 2014).

The R-ODS will be collected from subjects and recorded in the eCRF. For detailed administration timepoints, see Appendix A Schedule of Study Procedures and Assessments.

9.1.6.2.2 Medical Research Council Sum Score

The MRC sum score will serve as a measure of muscle strength (Kleyweg et al., 1991). To obtain an MRC sum score, the following muscles on each side of the body are examined and the strength of each muscle is rated according to the MRC scale: deltoids, biceps, wrist extensors, iliopsoas, quadriceps, and anterior tibialis. The MRC scale ranges from 0 to 5, where:

0 = no visible contraction;

1 = visible contraction without movement of the limb;

2 = movement of the limb but not against gravity;

3 = movement against gravity over (almost) the full range;

4 = movement against gravity and resistance; and,

5 = normal.

All scores from both left and right side of the body are summed to obtain the MRC sum score. The MRC sum score ranges from 0 (paralysis) to 60 (normal strength).

In the current study, the MRC scale will be applied to assess the disablity of subjects with MMN at the study site by the investigator/designee. Further details for assessments will be provided as a separate document. For detailed administration timepoints, see Appendix A Schedule of Study Procedures and Assessments.

9.1.6.2.3 Guy's Neurological Disability Scale (GNDS)

Guy's Neurological Disability Scale is a questionnaire which consists of 12 separate categories (4 to 8 questions per category). The categories include: cognition, mood, vision, speech, swallowing, upper limb function, lower limb function, bladder function, bowel function, sexual function, fatigue, and others.

In the current study, only 2 categories; upper limb function and the lower limb function will be used for assessment of the disability of subjects with MMN.

The severity of each subscale is graded from 0 (normal function) to 5 (total loss of function) based according to severity and impact on the individual.

The questionnaire is driven by patient interview and includes a scoring section.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. At each study visit, subjects will be asked whether they have taken any medication other than the study drug , and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, electrocardiogram (ECG), or physical examination abnormalities noted at screening, according to the judgment of the investigator. The condition (ie, diagnosis) should be described.

9.1.9 Procedures for Clinical Laboratory Samples

All clinical laboratory tests will be performed according to the laboratory's standard procedures. Reference ranges will be supplied by the laboratory and used to assess the results for clinical significance and out-of-range changes which may be associated with, or constitute, an AE. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

The investigator will assess each abnormal laboratory value as described in this section. In addition, the sponsor will evaluate laboratory values for abnormalities according to a 5-point (Grades 0-4) toxicity grading scale provided in Appendix D.

The Common Toxicity Criteria of the (Eastern Cooperative Oncology Group, 2006) will be used to grade the following laboratory values: alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), hemoglobin, lymphocytes, neutrophils, platelet count, serum creatinine, serum total bilirubin, and white blood cell (WBC) count. Grading for lactate dehydrogenase (LDH) will use the same thresholds as defined for ALT and AST. Sodium and potassium will be graded using the thresholds taken from the WHO toxicity grading system (World Health Organization, 2003).

The investigator's assessment of each abnormal laboratory value (with the exception of total IgG and specific antibodies) is to be recorded on the laboratory form. For each abnormal laboratory value, the investigator will determine whether the value is also considered an AE (see definition in Section 10.1.2). If yes, the sign, symptom, or medical diagnosis will be recorded on the AE eCRF. If the abnormal value was not deemed an AE because it was due to a laboratory error, was due to a pre-existing disease (Section 10.1.4), was not clinically significant, was a symptom of a new/worsened condition already recorded as an AE, or was due to another issue that will be specified, the investigator will record the justification on the laboratory form. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator. Any positive seroconversion result shall be retested and confirmed.

The standard amount of blood that will be drawn for each test per visit is 2.0 mL for hematology panel, 4.4 mL for clinical chemistry panel, 6.1 mL for serum IgG, 1.0 mL for hemoglobin A1c (HbA1c), 6.0 mL for anti-rHuPH20 antibodies, 1.1 mL for serum IgA, 11.2 mL for tests of HBsAG, HCV and HIV, 2.2 mL for serum iron, ferritin and total iron binding capacity (TIBC), 7.1 mL for hemolytic panel, 15.8 mL for immunogenicity panel, and 14.5 mL for backup, respectively. Some tests can use the same blood sampling tube and refer to the details in Appendix A for the total amount of blood sampling at each visit. The maximum amount of blood sampling per visit is approximately 58 mL at Epoch 1 Week 1. At the same visit, an additional blood sampling will be required for blood type test and the sampling volume depends on the study site.

9.1.9.1 Hematology and Clinical Chemistry

The hematology panel will consist of complete blood count (hemoglobin, hematocrit, erythrocytes [ie, red blood cell count], and leukocytes [ie, WBC]) with differential (ie, basophils, eosinophils, lymphocytes, monocytes, neutrophils) and platelet counts. In addition, absolute neutrophil counts will be determined by laboratory calculation.

The clinical chemistry panel will consist of sodium, potassium, chloride, bicarbonate, protein, albumin, ALT, serum total bilirubin, AST, ALP, LDH, BUN, serum creatinine, creatinine phosphokinase, glucose, haptoglobin, and lipase.

Immunoglobulin G will be measured for assessment of serum levels.

Blood will be obtained for assessment of hematology and clinical chemistry including IgG at distinct study visits, and at study completion/termination. For a schedule of laboratory test blood drawings, see Appendix A. These assessments will be performed on EDTA-anticoagulated whole blood and serum, respectively, processed through a central laboratory.

Glomerular Filtration Rate

For eligibility determination (exclusion criterion #11), serum creatinine obtained as part of the clinical chemistry panel will be used for the estimation of GFR according to the CKD-EPI creatinine equation (2009), as follows (Levey et al., 2009):

GFR = 141 × min(Scr/κ, 1)α × max(Scr/κ, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]

where Scr is serum creatinine (mg/dL)

κ = 0.7 if female
κ = 0.9 if male
α = -0.329 if female
α = -0.411 if male
min = The minimum of Scr/κ or 1
max = The maximum of Scr/κ or 1

9.1.9.2 Hemoglobin A1c

The HbA1c measurements will be performed to support eligibility determination. During the study, HbA1c will be measured at Epoch 1 Week 1 (E1W1), during the interim visit, and at the end of treatment visit of each treatment period (or during early termination visit in subjects who discontinue early on the study) to monitor glycemic control in these subjects.

9.1.9.3 Serum IgG

Serum IgG level at baseline visit will be recorded as the one-time snapshot value during IVIG treatment. During Epoch 1 and Epoch 2, trough serum IgG samples must be collected as scheduled on the day of the IP administration prior to the start of the infusion. Blood samples are to be collected and processed according to directions provided in the laboratory manual.

Each serum sample will be split into duplicate aliquots of approximately equal volume; one of which will serve as a retention (backup) sample.

Serum IgG trough levels must also be collected on each subject on or after Day 120 or at the time of CIDP symptom relapse/MMN symptom worsened.

9.1.9.4 Anti-rHuPH20 Antibodies

Plasma samples for the detection of anti-rHuPH20 binding and neutralizing antibodies will be collected at baseline (Epoch 1 Week 1 prior to IP administration), during early time course (at 2, 3-4, and 7-8 weeks since start of treatment), during the Epoch 1 interim visit (ie, at 13 to 15 weeks since start of treatment; the precise week of sample collection depends on the subject's dosing interval and scheduling), at the end of Epoch 1 treatment visit, during the Epoch 2 visit, and at the end of the first 6 months of Epoch 2 treatment visit (the precise week of sample collection depends on the subject's dosing interval and scheduling)/early termination visit/End of study visit (see Appendix A). Blood samples for the detection of anti-rHuPH20 binding neutralizing antibodies will be collected and processed according to directions provided in the laboratory manual. At each collection timepoint, plasma samples will be collected into separate K3EDTA tubes labeled for binding antibodies and neutralizing antibodies. Each will then be split into duplicate aliquots of approximately equal volume; one of which will serve as a retention (backup) sample. All subjects will be monitored for the formation of anti-rHuPH20 antibodies using validated anti-rHuPH20 antibody detection (ADA) assay (also known as the Screening and Confirmatory Binding Assay). Samples with antibody titers ≥1:160 will be analyzed for the presence of neutralizing antibodies using a validated assay based on neutralization of rHuPH20 activity. If it takes time to obtain the results of titers of the binding antibody measurement, the neutralizing antibody measurement and binding antibody measurement can be conducted simultaneously.

9.1.9.5 Serum IgA

Serum IgA level will be measured for the determination of eligibility. Serum IgA measurement will be performed at the central laboratory using an assay with a lower quantification limit of 8 mg/dL.

9.1.9.6 Specialty Tests

Specialty tests include: hepatitis B surface antigen, polymerase chain reaction (PCR) for HCV and PCR for HIV-1/2. For a schedule of laboratory test blood drawings, see Appendix A. These assessments will be performed at the central laboratory.

Additional specialty tests may be performed if required to establish the etiology of an AE or of abnormal laboratory results, such as tests for HIV, HAV, HBV, HCV, HEV, or B19V.

9.1.9.7 Urinalysis

Urinalysis includes: color, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase, and microscopic examination.

For a schedule of laboratory test sample drawings, see Appendix A. These assessments will be performed at the central laboratory. Local laboratory can be used if deemed necessary.

A urine pregnancy test will be performed at the study site for females of childbearing potential as indicated in Appendix A (see also Section 9.1.10).

9.1.9.8 Serum Iron, Ferritin, and Total Iron Binding Capacity

Serum iron, ferritin, and TIBC will be measured at Week 1 in Epoch 1. At any time during the study, the iron panel may be performed as part of AE/safety evaluation. Serum iron, ferritin, and TIBC tests will be performed at the central laboratory.

9.1.9.9 Hemolytic Panel

The first hemolytic panel will be measured at E1W1. The Hgb result obtained from the E1W1 will serve as the baseline Hgb value for the duration of the study. In case of absence of E1W1 result for any reason, screening Hgb result serve as the baseline Hgb value. Hemoglobin and LDH values can be taken from the hematology and clinical chemistry panels, if conducted on the same day as the hemolytic panel. For subsequent tests at Epoch 1, if there is a reduction in Hgb of ≥1 g/dL compared to baseline Hgb, every effort is to be made to perform a hemolytic panel within 72 hours. If it is not feasible to do so, the hemolytic panel must be performed as soon as possible but at the next scheduled visit, at latest. For the tests at Epoch 2, if there is a reduction in Hgb of ≥1 g/dL compared to Hgb value in previous data, every effort is to be made to perform a hemolytic panel as soon as possible but at the next scheduled visit, at latest. At any time during the study, an unscheduled hemolytic panel may be performed in the event of suspected hemolytic anemia. Any LDH test result of 2× ULN or greater will trigger analysis of the sample for LDH isoenzymes.

It is not necessary to repeat the hemolytic panel if the drop of ≥1 g/dL Hgb remains constant 72 hours after the first full dose of the IP or after an unscheduled visit blood draw, unless it drops further. It is recommended that the investigator uses good medical judgement in assessing subjects with an unexplained decrease in serum Hgb as other medical conditions beside hemolysis can cause this, and therefore may require additional investigations. The hemolytic anemia panel will consist of Hgb, LDH, serum haptoglobin, plasma-free (unbound) Hgb, serum direct anti-globulin (direct Coombs) test (in the event of positive direct Coombs test, antibody elution test is recommended to be performed, or comprehensive judgement is to be made on the clinical importance of the positive result based on the shift of Hgb and LDH values at pre-/post-

Coombs test if the antibody elution test cannot be performed), reticulocyte count, as well as urine hemosiderin.

Hemolytic tests will be performed at the central laboratory or other laboratories as appropriate (eg, antibody elution test is to be performed if possible in the event of positive direct Coombs test). Complete hematology and clinical chemistry assessments may be performed in order to obtain laboratory results required for a hemolytic panel.

9.1.9.10 Immunogenicity Panel

At E1W1 predose, samples will be collected for the following tests to be conducted: 50% hemolytic complement activity of serum (CH50), serum complement component 3 (C3), serum complement component 4 (C4), C1q binding assay, and circulating immune complex (CIC) Raji cell assay.

At any time during the course of the study, subjects who have (a) two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers at E1W1, and (b) a moderate or severe AE which may be a result of immune-mediated response to either immunoglobulin, rHuPH20, or other concomitant medications (see Table 9-1) will be asked to return to the study site as soon as possible to undergo an additional pane of testing outlined in Table 9-2.

For a schedule of laboratory test blood drawings, see Appendix A.

Table 9-1. List of Conditions/Symptoms Which May be a Result of Immune-Mediated Response to Either Immunoglobulin, rHuPH20, or Other Concomitant Medications

Allergic reactions • Urticaria • New-onset bronchospasm • Oedema of tongue, lips, face (angioedema) • Anaphylaxis • Stevens-Johnson syndrome • Erythema multiforme • Toxic epidermal necrolysis
Immune complex mediated reactions – Local • Induration/nodule at the site of administration that persists for more than 48 h • Excessive inflammation at the site of administration - severe redness, heat, swelling, and/or pain • Tissue necrosis/ulceration at the site of administration • Dystrophic or fibrotic changes at the site of administration • Pigmented skin changes at the site of drug administration
Immune complex mediated reactions – Systemic

Table 9-1. List of Conditions/Symptoms Which May be a Result of Immune-Mediated Response to Either Immunoglobulin, rHuPH20, or Other Concomitant Medications

• Arthritis • Vasculitis (purpuric rash) • Glomerulonephritis - hematuria, red cell casts in urine, progressive renal dysfunction

Table 9-2. Immunogenicity Panel

1.	Repeat test for anti-rHuPH20 binding antibody titers
2.	Test (or repeat test, as applicable) for the presence of neutralizing anti-rHuPH20 antibodies
3.	Assessment of cross reactivity to human HYAL1, HYAL2, and HYAL4- only for subjects whose anti-rHuPH20 binding antibody titer exceeds 1:10,000
4.	Hematology panel with manual differential (see Section 9.1.9.1)
5.	Clinical chemistry panel (see Section 9.1.9.1)
6.	CH50
7.	Serum C3
8.	Serum C4
9.	C1q binding assay
10.	CIC Raji cell assay
11.	Blood draw for additional testing as necessary

9.1.10 Contraception and Pregnancy Avoidance Procedure

9.1.10.1 Definitions and Procedures for Contraception and Pregnancy Avoidance

Sexually active females of childbearing potential should use an acceptable form of contraception. Females of childbearing potential must be advised to use acceptable contraceptives throughout the study period and for 30 days following the last dose of the study drug. If used, hormonal contraceptives should be administered according to the package insert. Any female of childbearing potential who is not currently sexually active must agree to use acceptable contraception, as defined below, if she becomes sexually active during the study and for 30 days following the last dose of the study drug.

Female subjects should be either:

- Premenarchal and either Tanner stage 1 or less than age 9 years, or
- Postmenopausal (12 consecutive months of spontaneous amenorrhea and age ≥51 years)

- Surgically sterile (having undergone one of the following surgical acts: hysterectomy, bilateral tubal ligation, bilateral oophorectomy or bilateral salpingectomy) and at least 6 weeks post-sterilization, or
- Of childbearing potential with a negative urine human chorionic gonadotropin (hCG) or serum beta-hCG (β-hCG) pregnancy test at the screening visit. Females of childbearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception include the following:

- Intrauterine devices plus condoms
- Hormonal contraceptives (oral), stabilized for at least 30 days prior to the baseline visit, plus condoms. Note: If the subject becomes sexually active during the study, she should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

9.1.10.2 Contraceptive Guidance

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described below.

Highly Effective Contraceptive Methods That Are User Dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] ➢ Oral
Highly Effective Methods That Are User Independent[a]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b] ➢ Intrauterine device ➢ Intrauterine hormone-releasing system ➢ Bilateral tubal occlusion
• Vasectomized partner A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
• Sexual abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
NOTES:

a) Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b) Hormonal contraception may be susceptible to interaction with the study treatment, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the treatment period and for at least 30 days after the last dose of study treatment

9.1.11 Pregnancy

A urine pregnancy test will be performed at the study site for females of childbearing potential as indicated in Appendix A.

All pregnancies are reported from the time informed consent is signed until the end of study (EOS)/early termination visit.

Any report of pregnancy for any female study participant must be reported within 24 hours of the Investigator's awareness, using a pregnancy notification form (see Appendix E).

A copy of the Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the Contract Research Organization (CRO) medical monitor using the details specified in the Appendix E. The pregnant female subject must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days and 1 year post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage, elective abortion or congenital abnormality are considered SAEs and must be reported using the Safety Report Form.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported in the Safety Report Form as well in the Pregnancy Report Form. The test date of the first positive urine hCG or serum β-hCG test or ultrasound result will determine the pregnancy onset date.

9.1.12 ECG Procedure

A 12-lead ECG will be performed at screening for the determination of eligibility (eg, exclusion of clinically significant cardiac abnormalities, such as unstable cardiac arrhythmias, and detection of other clinically significant cardiac abnormalities that may indicate an underlying condition that may impede the subject's participation in the study, pose increased risk to the subject, or confound the results of the study). A 12-Lead ECG will be also performed at the end of Epoch 1/the first 6 months of Epoch 2 visit, end of study visit or early termination visit. The

investigators will interpret the ECG using 1 of the following categories; "within normal limits", "abnormal, not clinically significant", or "abnormal, clinically significant". Changes in ECG findings should be judged by investigators (see details in section 10.1.4).

9.1.13 Guidance on Reporting and Assessing rHuPH20 (hyaluronidase) antibody test results

All hyaluronidase antibody test results (titers, and binding or neutralizing) will be assessed for clinical significance by the investigator in the electronic data capture (EDC) database but are not to be reported as AEs. For AEs occurring during the subcutaneous infusion of hyaluronidase the investigator and sponsor will independently assess relatedness, also taking into account quantitative and qualitative test results for hyaluronidase antibodies. For AEs occurring upon or after subsequent subcutaneous infusion of the immunoglobulin component an assessment of causality is confounded by the presence of the consecutively administered investigational product. The overlap is transient due to the short half-life of hyaluronidase of about 30 minutes in the SC space. The investigator and sponsor will independently evaluate the relatedness of an AE to one or the other component during this period.

9.1.14 Backup Samples/Biobanking

Backup samples should be taken and stored short-term (no more than 2 years after the final study report has been completed) appropriately for repeat or additional analysis, if necessary. These samples may be used for re-testing, further evaluation of an AE, or follow-up of other test results. The following samples are planned:

- Trough serum IgG samples (backup aliquots)
- Anti-rHuPH20 binding antibody samples (backup aliquots)
- Anti-rHuPH20 neutralizing antibody samples (backup aliquots)
- Plasma retention samples
- Serum retention samples

Additionally, Baseline and end-of-trial/Epoch serum samples will be stored for possible testing of pathogens identified in the future for no more than 2 years after the final study report has been completed.

For detailed sampling timepoints, see Appendix A.

Backup samples that remain after study testing is done may be stored and used for additional testing (eg, further evaluation of an abnormal test, investigation of an AE or suspected

seroconversion). Samples will be stored in a coded form for no more than 2 years after the final study report has been completed and then the samples will subsequently be destroyed.

9.1.15 Documentation of Screen Failure

Investigators must account for all subjects who sign informed consent.

A screen failure is a subject who has given informed consent and failed to meet all inclusion criteria and/or has met at least 1 of the exclusion criteria and has not been administered study drug. If the subject is withdrawn at the screening visit, the investigator should complete the eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE
- Did not meet inclusion criteria or did meet exclusion criteria.
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal.
- Study termination.
- Other.

Subject identification numbers assigned to subjects who fail screening should not be reused.

Subjects may be rescreened only once. Subjects who have failed screening based on the following reasons may be rescreened, after the cause underlying the initial screen failure has been resolved:

1. Subjects whose ineligibility is associated with a time period specified in the Inclusion Criteria (see Section 7.1) or Exclusion Criteria (see Section 7.2)
    - Inclusion criterion# 4: Changes to IVIG dose and/or dosing interval within 12 weeks prior to screening.
    - Exclusion criterion # 19/20: the subject has received or is currently receiving treatment with any immunomodulatory/immunosuppressive agents within 6 months prior to screening, or corticosteroids dose within 8 weeks prior to screening, regardless of indication.

- Exclusion criterion #21: Recently treated with previous PE within 3 months prior to screening.
- Exclusion criterion #24: Recent participation in another clinical study involving a study drug or investigational device within 30 days prior to enrollment

2. Subjects with screening laboratory abnormalities meeting exclusion criterion #17.
3. Subjects who have been erroneously determined to be ineligible to participate in this study.
4. Subjects with other reasons for initial screen failure may be rescreened at the discretion of the investigator.

All subjects must sign a new ICF prior to rescreening procedures. Subjects who are rescreened will be assigned a new subject identification number and new eCRFs are required for that subject.

9.2 Monitoring Subject Treatment Compliance

For study procedures that are to be performed under the direct supervision of the investigator/healthcare professional (eg, infusion nurse) at the study site or infusion center, no separate procedures will be used to monitor subject compliance.

Training, evaluation, and verification of the subject's (and/or caregiver's) proficiency in performing self-infusion procedures by the investigator/designee, must be documented as a prerequisite before the subject (and/or caregiver) will be allowed to begin self-administration of SC infusions. A healthcare professional (eg, infusion nurse) may be present to observe the subject's self-administration. All supplies used to administer study drug to the subject will be recorded on the eCRFs.

If subject perform self-administration at home, information (date/time of infusion, infusion site, infusion rate/volume, AE) will be recorded in subject's paper diary.

9.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Appendix A. Assessments should be completed at the designated visit/time point(s).

9.3.1 Screening Period (Screening and Baseline visits)

Subjects will be screened within 8 weeks prior to the first SC administration of TAK-771 in accordance with predefined inclusion and exclusion criteria as described in Section 7. (See also Section 9.1.15 for procedures for documenting screening failures).

Subjects will continue to receive their own IVIG treatment at the same dose and dosing interval as prescribed prior to their entry into this study.

Procedures to be completed at Screening visit (within 6 weeks prior to baseline visit) after obtaining the written informed consent include:

- Demographics, medical history, and medication/non-drug therapy history
- Physical examination
- Body weight, height, and BMI.
- INCAT disability scale only for eligibility determination of CIDP subjects
- 12-Lead ECG
- Laboratory
- Concomitant conditions and medications.

The baseline visit will take place on the day of the subject's last IVIG infusion (2 weeks before receiving the first infusion of study drug). Procedures to be completed at the baseline visit include:

- To check screening test results (should be performed before the other procedures for the baseline visit)
- last IVIG infusion
- Vital signs.
- Clinical assessments (eg, INCAT disability scale [for CIDP subjects], Grip strength etc., R-ODS, and MRC sum score and GNDS [for MMN subjects]).
- Serum IgG.
- Concomitant conditions and medications.

9.3.2 Treatment Period

Epoch 1

Eligible subjects will receive TAK-771 for a period of 6 months or until relapse. The dosing interval should be determined to be either every 2, 3, or 4 week based on the previous IVIG treatment. Even if the dosing interval is converted, the dose should be maintained the same monthly equivalent IgG dose.

The number of infusion visits during the SC treatment period will vary across subjects, depending on whether their infusion cycles are every 2, 3, or 4 weeks. Adjustment to dosing interval is not allowed, except due to intolerability.

The first SC administration of TAK-771 will take place 2 weeks (±3 days) following the last IVIG administration. To gradually increase the SC infusion volume, a dose ramp-up schedule will be utilized until the subject's full dose is reached.

The SC infusions during the ramp-up period and, at a minimum, the first full dose infusion will be administered under direct supervision at the study site or infusion center to monitor for safety and tolerability. In addition, this will allow for the determination of the infusion rate and infusion volume per infusion site that can be tolerated by the subject. At the investigator's discretion, the remainder of the SC infusions may then take place at the study site, infusion center, or at the subject's home or other suitable location, as acceptable per local regulations and standard practices of the study site. Subjects (or caregiver) who is well-experienced in self-administration can administer TAK-771 at home at the discretion of investigators if IRBs approved, with remote video monitoring by HCPs if it needed.

Procedures and assessments to be completed include:

Cohort 1 (CIDP)

- INCAT disability score.
- R-ODS.
- Hand grip strength.

Cohort 2 (MMN)

- Hand Grip strength (baseline measurement point, investigators judges which of both hands is more affected).
- MRC sum score (Measurement site (both sides): shoulder abductor muscle, elbow flexor, elbow extension muscle, hand joint flexor, hand joint extension muscle, hip flexor, knee flexor, knee extension muscle, dorsum of foot flexor, sole of foot flexor).
- GNDS
- R-ODS

Cohort 1 (CIDP) and Cohort 2 (MMN)

- Serum IgG levels.

- Trough serum IgG levels (prior to the start of the infusion).
- anti-rHuPH20 antibodies.
- Vital Signs.
- Physical Examination.
- Weight and BMI.
- Laboratory tests.
- Infusion Self-administration proficiency checklist.
- AEs.

See Appendix A for detailed measurement timepoints.

Epoch 2

The number of infusion visits during the SC treatment period will vary across subjects, depending on whether their infusion cycles are every 2, 3, or 4 weeks. After the first 6 months of Epoch 2, the subject who is well-tolerating and voluntarily wishes to continue TAK-771 administration can stay in the Epoch 2 (continued) until the commercial TAK-771 is available in each study site. Subjects (or caregiver) who is well-experienced in self-administration can administer TAK-771 at home under remote video monitoring by HCPs at the discretion of investigators if IRBs approved, with remote video monitoring by HCPs if it needed. Symptoms and laboratory data will be assessed once per 3 months (See Appendix A for detailed measurement timepoints).

9.3.3 Unscheduled Visit for Relapse Assessment

At any time during the SC treatment period in Epoch 1 or Epoch 2, unscheduled visit(s) to the study site will be allowed for subjects who experience CIDP worsening to perform INCAT, R-ODS, hand grip strength, and will be allowed for subjects who experience MMN worsening to perform hand grip strength, MRC sum score, GNDS, and R-ODS assessments.

9.3.4 Final Visit or Early Termination

Epoch 1

Subjects may complete the entire 6-month SC treatment period without relapse. End-of-Epoch 1 (EOE1) assessments are to be conducted on the day of the first infusion in the Epoch 2. This will mark the subjects' completion of the Epoch 1. If withdrawal or discontinuation occurred (see Section 7.4), the last assessments are to be performed at the early termination (ET) visit which is at the end of treatment, and Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes

first.

Epoch 2

Subjects may complete the first 6-month SC treatment period without relapse. End of the first 6 months of Epoch 2 assessments are to be conducted. If the subject wishes to receive TAK-771 with good tolerability, TAK-771 can be continuously administered until the commercial TAK-771 is available in each study site or study termination by the sponsor or regulatory agencies, on which End of Study assessment will mark.

If withdrawal or discontinuation occurred (see Section 7.4), the last assessments are to be performed at the early termination visit. Recovering/resolving AEs will be followed until resolution, medically stabilized, or 30 days after the study completion/termination visit, whichever comes first.

9.3.5 After Study Care

Study drug will not be available upon completion of the subject's participation in the study. The subject should be returned to the care of a physician and standard therapies as required.

10. PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

10.1.3 Treatment-emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the treatments or any event already present that worsens in either intensity or frequency following exposure to the treatments.

10.1.4 Additional Points to Consider for Pretreatment Events and Adverse Events

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs.)
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

Pretreatment events/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (eg, asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (eg "worsening of…").
- If a subject has a degenerative concurrent medical condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in intensity of AEs /Serious PTEs:

- If the subject experiences changes in intensity of an AE/serious PTE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (eg, as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs, but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action, should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.5 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in DEATH.
2. Is LIFE THREATENING.
   - The term "life threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
   - May require intervention to prevent items 1 through 5 above.
   - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

Pretreatment events that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (see Sections 10.2.2 and 10.3).

10.1.6 Intensity of Pretreatment Events and Adverse Events

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of Adverse Events

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or investigator.

The start date of PTEs/AEs will be determined using the following criteria;

PTEs/AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms/diseases were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.
Worsening or complication of concurrent medical conditions or any signs/symptoms/diseases before treatment	The date that a worsening or complication of the condition was noted first by the subject and/or the investigator should be recorded.
The examination after start of the study drug showed abnormal values/findings.	The date of examination when an abnormal value or findings that was judged to be clinically significant was noted should be recorded.
The examination at the start of the study drug showed abnormal values/findings and the subsequent examinations showed worsening of the symptoms.	The date of examination when apparent elevation, reduction, increase or decrease was confirmed in judgment according to the trends in those values or findings should be recorded.

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11 Frequency

Episodic AEs/PTE (eg, vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE eg, the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcome

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved, but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of Adverse Events

10.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered study drug or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time the subject signs the informed consent to participate in the study. Routine collection of AEs will continue until final visit/ early termination.

10.2.1.2 PTE and AE Reporting

At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study. Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term.
2. Start and stop date and time.
3. Frequency.
4. Intensity.
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs).
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure.
7. Action concerning study drug (not applicable for PTEs).

8. Outcome of event.
9. Seriousness.

The investigator become aware of a potential AE through the information collected with this instrument, proper follow-up with the patient for medical evaluation should be undertaken. Through this follow-up if it is determined that an AE not previously reported has been identified, normal reporting requirements should be applied.

10.2.2 Collection and Reporting of Serious Adverse Events

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE should be reported by the investigator to the sponsor/the Emergency Reception Center for Safety Information (see Appendix E) within 24 hours/1 business day of the SAE occurrence, along with any relevant information. The investigator should submit the detailed SAE Form to the sponsor/the Emergency Reception Center for Safety Information appropriate personnel (see Appendix E) within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

A short description of the event and the reason why the event is categorized as serious.

- Subject identification number.
- Investigator's name.
- Name of the study drug(s)
- Causality assessment.

The investigator should submit the original copy of the SAE form to the sponsor.

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation.

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the investigators and IRBs/the head of the study site, as applicable. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor-supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11. STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

12. DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 CRFs (Electronic)

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English. Data are transcribed directly onto eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by Takeda personnel (or designees) and will be answered by the site.

Corrections to eCRFs are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

All data will have separate source documentation; no data will be recorded directly onto the eCRF.

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

Electronic CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

The investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 3 years after the date of notification in the case that the investigation is discontinued.)
2. The day 3 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

Since the investigational drug (SCIG, 20%) in this study is equivalent to the specified biological products, the records regarding the administration of SCIG, 20% at the study sites must be maintained for 20 years according to the regulation of the product of specified biological products “Explanation of the use of specified biological products to the target person and records and preservation of specified biological products” (Pharmaceutical Affairs No. 0515012 May 15, 2003).

13. STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 Analysis Sets

- Full Analysis Set (FAS): All enrolled subjects who received TAK-771 at least once, this will be the efficacy analysis set.
- Safety analysis set: All enrolled subjects who received TAK-771 administration at least once, this will be the safety analysis set.
- Per Protocol Set (PPS): All enrolled subjects who received TAK-771 at least once, and had no major protocol deviations that may have a significant impact on the primary endpoint. Such protocol deviations will be determined prior to End of Epoch 1; PPS will be used for sensitivity and/or supportive analyses.

Although efficacy data will be assessed for CIDP and MMN independently, safety will be assessed as integrated data from CIDP and MMN subjects. Data for the 2 Epochs will be presented separately.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Baseline characteristics and demographic variables will be summarized for FAS.

13.1.3 Efficacy Analysis

13.1.3.1 Primary Endpoint (Epoch 1 only)

Cohort 1 (CIDP)

Occurrence of relapse (worsening of functional disability defined as an increase of >1 point relative to the pre-SC treatment baseline score in adjusted INCAT disability score) and corresponding exact 2-sided Clopper-Pearson 95% CI will be provided based on the FAS. Missing outcomes will be imputed as no relapse. The efficacy would be shown in the case that the upper bound of 95% CI for the relapse rate would be below the threshold of 57%.

Cohort 2 (MMN)

The mean change from baseline in maximum grip strength will be presented for more affected hand using descriptive statistics and 2-sided 95% CI based on the FAS. A detailed explanation for how to handle missing data and intercurrent events will be described in the SAP.

The mean maximum grip strength will be compared with the values from the literatures for the intended study but no formal statistical comparisons will be conducted. Individual cases will be also evaluated in detail since there will be only be a few cases.

13.1.3.2 Secondary Endpoint

Clinical worsening of CIDP, defined as one or more of the following: subject relapse; ≥8 kPa decrease in the hand grip strength in the more affected hand; ≥4 points decrease in R-ODS relative to the pre-SC treatment baseline score at 2 consecutive timepoints (the time of withdrawal from the SC treatment period), will be analyzed using the same methods as the primary endpoint.

Time to relapse, defined as time from the date of the first SC administration of TAK-771 to the date of relapse will be calculated and cumulative incidence will be estimated using the Kaplan-Meier method and displayed graphically.

The mean change in R-ODS score, activities of daily living (ADL), from baseline to the end of the treatment period will be analyzed using descriptive statistics and 2-sided 95% CI. The last non-missing change will be used from subjects who discontinued early, ie, the last observation carried forward (LOCF) will be used. These analyses will be performed in the FAS.

The secondary endpoints associated to Cohort 2 (MMN), GNDS in upper limb and lower limb categories, will be descriptively analyzed as a binary variable indicating whether the score of a subject deteriorated from baseline to the value at each post baseline.

The secondary endpoints associated to Cohort 2 (MMN), ie, change from baseline to 6 months after IP administration in MRC sum score will also be analyzed according to the methods for the primary endpoint.

The secondary endpoints associated to Cohort 1(CIDP) and Cohort 2 (MMN), change from baseline in an average of handgrip strength of both hands, will be analyzed according to the methods for the primary endpoint.

13.1.4 Pharmacokinetic Analysis

Trough plasma concentrations of IgG will be summarized for the Safety set, using descriptive statistics: number of subjects with evaluable sample, mean, standard deviation (SD), median, minimum, maximum, geometric mean, and SD of the geometric mean.

13.1.5 ADA Analysis

Subjects are defined as having elevated rHuPH20 antibody titers if they have two consecutive anti-rHuPH20 antibody titers of ≥1:160 which are elevated from the subject's baseline titers. If at

least 5 subjects have elevated titers, then an exploratory analysis will be conducted to assess if there is any evidence of relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs.

In addition, an exploratory analysis of any treatment emergent abnormal titer or rises above baseline in anti-rHuPH20 antibody titer will be performed to assess if there is any evidence of relationship between anti-rHuPH20 antibody titer (elevated, not elevated) and the occurrence of AEs.

13.1.6 Safety Analysis

Adverse events will be summarized using the safety analysis set. No statistical testing or inferential statistics will be generated. Safety data will be summarized descriptively.

All AEs will be coded using MedDRA. Data will be summarized using preferred term and primary system organ class.

Clinically significant, treatment-emergent changes in physical exams, vital signs, ECGs, and clinical laboratory measurements will be recorded as AEs; therefore, safety analyses will be primarily based on analysis of AEs, including ARs plus suspected ARs. Safety endpoints will be summarized descriptively in Epoch 1 safety set using actual treatment.

Treatment-emergent AEs (TEAEs), serious TEAEs, and other AE-related endpoints will be described by the number and percentage of subjects who experienced a particular type of event. Additionally, event rates will be expressed as number of events (reports) per infusion, per subject, and per subject-year.

Both systemic event and events that are localized to the infusion site(s) will be examined. The relationship of AEs to infusions will be described further in terms of the number and proportion of infusions that were associated with an AE, and the number and proportion of infusions that were not completed as planned (interrupted, discontinued) due to an AE.

Infusion site swelling following SC infusion that is reported by subjects will be captured and reported as AEs.

For laboratory measurements, data will be summarized time point. Summaries of continuous measurements will include number of subjects, mean, SD, minimum, and maximum. For categorical measurements, the proportion of observations in each category will be presented.

13.2 Interim Analysis and Criteria for Early Termination

Two formal interim data analysis to support the Japanese New Drug Application submission will be completed. Both will summarize efficacy and safety of treatment with TAK-771 in Japanese subjects with CIDP/MMN. The first interim analysis will be conducted when the last subject has reached the End of Epoch 1 visit. The second interim analysis will be conducted when the last subject has reached the visit of Week 24 in Epoch 2. The target data shall be all data obtained until each interim analysis. The first and the second interim clinical study reports summarizing data will be prepared based on these results of analyses. No adaptive design or data monitoring committee is planned for this study.

13.3 Determination of Sample Size

Cohort 1 (CIDP)

The latest meta-analysis (Lewis et al., 2020) reported that 43% of placebo-treated patients showed no deterioration in 5 placebo-controlled clinical studies, hence the estimated relapse rate in placebo-treated patients of 57%. The estimated relapse rate of Cohort 1 is 12% based on the average relapse rate in 2 clinical trials (13% in ICE study and 10% in the PATH extension study). As a result, the estimated sample size to show a statistically significant (at the 2.5% level) lower relapse rate than 57% with about 90% power would be 16 CIDP patients based on an assumed TAK-771 relapse rate of 12% and assuming a 15% dropout rate using a 95% two-sided Clopper-Pearson CI. This sample size was calculated based on simulation results from 100,000 trials.

Cohort 2 (MMN)

The target number of MMN subjects was determined based on feasibility given the inclusion and exclusion criteria for this study. Multifocal motor neuropathy is less prevalent than CIDP. The annual number of MMN patients in Japan is estimated to be about 400 cases (Matsui, 2012). Five subjects are scheduled to be included in this study. Since this study is planned to be conducted in parallel with the clinical trial of maintenance therapy with CIDP patients, an effort would be made to recruit additional subjects until enrollment period of CIDP study ends, even if enrollment of 5 subjects is completed.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and head of the study site guarantee access to source documents by the sponsor or its designee (contract research organization) and by the IRB. In case alternative approaches are needed due to COVID-19 or unavoidable circumstances, data monitoring may be conducted remotely (eg, video calls/conferences and telephones). The Remote Monitoring strategy is provided in the Clinical Operation Plan.

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information if separate from the informed consent forms, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to study subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (eg, the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency).

If the study site is contacted for an inspection by a regulatory agency, the sponsor should be notified immediately. The investigator and study site/head of the study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15. ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants (ie, subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix B. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for ICF and investigator responsibilities.

15.1 IRB Approval

Institutional Review Boards must be constituted according to the applicable country/local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB. If any member of the IRB has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB for the protocol's review and approval. This protocol, the IB, a copy of the ICF, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB for approval. The IRB's written approval of the protocol and subject ICF must be obtained and submitted to the sponsor or designee before commencement of the study (ie, before shipment of the sponsor-supplied drug or study specific screening activity/signing a contract for the clinical study). The IRB approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (eg, ICF) reviewed; and state the approval date. The sponsor will ship drug/notify site once the sponsor has confirmed the adequacy of site regulatory documentation. Until the site receives drug/notification, no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB, and submission of the investigator's final status report to IRB. All IRB approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of ICF as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal data and personal health information for purposes of conducting the study. The ICF and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date ICF is given. The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB approval of the ICF and if applicable, the subject authorization form. The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB and the sponsor prior to use.

The ICF, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the ICF, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event the subject is not capable of rendering adequate written ICF, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the ICF and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the ICF and subject authorization (if applicable) at the time of consent and prior to subject entering into the study.

Once signed, the original ICF, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the ICF in the subject's medical record. Copies of the signed ICF, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised ICF must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised ICF.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (see Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (ie, subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with facility name, investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.4.4 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to study subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16. REFERENCES

Berger, M. 2004. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol,* 112**,** 1-7.

Berger, M., Jolles, S., Orange, J. S. & Sleasman, J. W. 2013. Bioavailability of IgG Administered by the Subcutaneous Route. *J. Clin. Immunol,* 33**,** 984-990.

Cocito, D., Grimaldi, S., Paolasso, I., Falcone, Y., Antonini, G., Benedetti, L., Briani, C., Fazio, R., Jann, S., Mata, S., Sabatelli, M., Nobile-Orazio, E. & The Italalian Network for CIDP Register 2011. Immunosuppressive treatment in refractory chronic inflammatory demyelinating polyradiculoneuropathy. A nationwide retrospective analysis. *Eur. J. Neurol,* 18**,** 1417-1421.

Cocito, D., Merola, A., Peci, E., Mazzeo, A., Fazio, R., Francia, A., Valentino, P., Liguori, R., Filosto, M., Siciliano, G., Clerici, A. M., Lelli, S., Marfia, G. A., Antonini, G., Cecconi, I., Nobile-Orazio, E., Lopiano, L. & SCIg and Chronic Dysimmune Neuropathies Italian Network 2014. Subcutaneous immunoglobulin in CIDP and MMN: A short-term nationwide study. *J Neurol,* 261**,** 2159-2164.

Dalakas, M. C. 2011. Advances in the diagnosis, pathogenesis and treatment of CIDP. *Nat. Rev. Neurol,* 7**,** 507-517.

Draak, T. H., Vanhoutte, E. K., van Nes, S. I., Gorson, K. C., Van der Pol, W. L., Notermans, N. C., Nobile-Orazio, E., Leger, J. M., Van den Bergh, P. Y., Lauria, G., Bril, V., Katzberg, H., Lunn, M. P., Pouget, J., van der Kooi, A. J., Hahn, A. F., van Doorn, P. A., Cornblath, D. R., van den Berg, L. H., Faber, C. G. & Merkies, I. S. 2014. Changing outcome in inflammatory neuropathies: Rasch-comparative responsiveness. *Neurology,* 83**,** 2124-2132.

Dyck, P. J., Daube, J., O'Brien, P., Pineda, A., Low, P. A., Windebank, A. J. & Swanson, C. 1986. Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. *N Engl J Med,* 314**,** 461-465.

Eastern Cooperative Oncology Group 2006. Common toxicity criteria of the Eastern Cooperative Oncology Group. [Accessed 27 Mar 2024]: https://web.archive.org/web/20131010202240/http://ecog.dfci.harvard.edu/general/ctc.pdf.

Eftimov, F., Vermeulen, M., de Haan, R. J., van den Berg, L. H. & van Schaik, I. 2009. Subcutaneous immunoglobulin therapy for multifocal motor neuropathy. *J Peripher Nerv Syst,* 14**,** 93-100.

Eftimov, F., Vermeulen, M., van Doorn, P. A., Brusse, E., van Schaik, I. N. & PREDICT Study Group 2012. Long-term remission of CIDP after pulsed dexamethasone or short-term prednisolone treatment. *Neurology,* 78**,** 1079-1084.

European Federation of Neurological Societies 2010. Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy, Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society - First Revision. *J Peripher Nerv Syst,* 15**,** 1-9.

European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of multifocal motor neuropathy: 2010. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society--First Revision. *J. Peripher. Nerv. Syst,* 15**,** 295-301.

Gardulf, A., Andersen, V., Björkander, J., Ericson, D., Frøland, S. S., Gustafson, R., Hammarström, L., Jacobsen, M. B., Jonsson, E., Möller, G., Nyström, T., Søeberg, B. & Smith, C. I. E. 1995. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. *Lancet,* 345**,** 365-369.

Gardulf, A., Björvell, H., Gustafson, R., Hammarström, L. & Smith, C. I. 1993. Safety of rapid subcutaneous gammaglobulin infusions in patients with primary antibody deficiency. *Immunodeficiency,* 4**,** 81-84.

Gardulf, A. & Hammarström, L. 1996. Subcutaneous administration of immunoglobulins. What are the advantages? *Clin Immunother* [Online], 6 (2) 108-116. [Accessed 27 Mar 2024]: https://link.springer.com/content/pdf/10.1007/BF03259507.pdf.

Gardulf, A., Hammarström, L. & Smith, C. I. 1991. Home treatment of hypogammaglobulinaemia with subcutaneous gammaglobulin by rapid infusion. *Lancet,* 338**,** 162-166.

Gorson, K. C. 2012. An update on the management of chronic inflammatory demyelinating polyneuropathy. *Ther. Adv. Neurol. Disord,* 5**,** 359-373.

Hahn, A. F., Bolton, C. F., Pillay, N., Chalk, C., Benstead, T., Bril, V., Shumak, K., Vandervoort, M. K. & Feasby, T. E. 1996. Plasma-exchange therapy in chronic inflammatory demyelinating polyneuropathy: a double-blind, sham-controlled, cross-over study. *Brain,* 119**,** 1055-1066.

Harbo, T., Andersen, H., Hess, A., Hansen, K., Sindrup, S. H. & Jakobsen, J. 2009. Subcutaneous versus intravenous immunoglobulin in multifocal motor neuropathy: a randomized, single-blinded cross-over trial. *Eur. J. Neurol,* 16**,** 631-638.

Harbo, T., Andersen, H. & Jakobsen, J. 2010. Long-term therapy with high doses of subcutaneous immunoglobulin in multifocal motor neuropathy. *Neurology,* 75**,** 1377-1380.

Hughes, R., Bensa, S., Willison, H., van den Bergh, P., Comi, G., Illa, I., Nobile-Orazio, E., van Doorn, P., Dalakas, M., Bojar, M., Swan, A. & Inflammatory Neuropathy Cause and Treatment (INCAT) Group 2001. Randomized controlled trial of intravenous immunoglobulin versus oral prednisolone in chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol,* 50**,** 195-201.

Hughes, R. A. 2003. Management of chronic inflammatory demyelinating polyradiculoneuropathy. *Drugs,* 63**,** 275-287.

Hughes, R. A., Donofrio, P., Bril, V., Dalakas, M. C., Deng, C., Hanna, K., Hartung, H. P., Latov, N., Merkies, I. S., van Doorn, P. A. & ICE Study Group 2008. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial. *Lancet Neurol,* 7**,** 136-144.

Iijima, M., Koike, H., Hattori, N., Tamakoshi, A., Katsuno, M., Tanaka, F., Yamamoto, M., Arimura, K., Sobue, G. & The Refractory Peripheral Neuropathy Study Group of Japan 2008. Prevalence and incidence rates of chronic inflammatory demyelinating polyneuropathy in the Japanese population. *J Neurol Neurosurg Psychiatr,* 79**,** 1040-1043.

Japanese Society of Neurology. *Clincial questions 7-8 and 7-9* [Online]. [Accessed 27 Mar 2024]: https://www.neurology-jp.org/guidelinem/cidp.html.

Kleyweg, R. P., van der Meche, F. G. & Schmitz, P. I. 1991. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. *Muscle Nerve,* 14**,** 1103-1109.

Köller, H., Kieseier, B. C., Jander, S. & Hartung, H. P. 2005. Chronic inflammatory demyelinating polyneuropathy. *N Engl J Med,* 352**,** 1343-1356.

Kuwabara, S., Misawa, S., Mori, M., Tamura, N., Kubota, M. & Hattori, T. 2006. Long term prognosis of chronic inflammatory demyelinating polyneuropathy: a five year follow up of 38 cases. *J Neurol Neurosurg Psychiatr,* 77**,** 66-70.

Kuwabara, S., Mori, M., Misawa, S., Suzuki, M., Nishiyama, K., Mutoh, T., Doi, S., Kokubun, N., Kamijo, M., Yoshikawa, H., Abe, K., Nishida, Y., Okada, K., Sekiguchi, K., Sakamoto, K., Kusunoki, S., Sobue, G. & Kaji, R. 2017. Intravenous immunoglobulin for maintenance treatment of chronic inflammatory demyelinating polyneuropathy: a multicentre, open-label, 52-week phase III trial. *Journal of Neurology, Neurosurgery & Psychiatry,* 88**,** 832-838.

Léger, J. M., de Bleecker, J. L., Sommer, C., Robberecht, W., Saarela, M., Kamienowski, J., Stelmasiak, Z., Mielke, O., Tackenberg, B., Shebl, A., Bauhofer, A., Zenker, O., Merkies, I. S. J. & PRIMA study investigators 2013. Efficacy and safety of Privigen® in patients with chronic inflammatory demyelinating polyneuropathy: Results of a prospective, single-arm, open-label phase III study (the PRIMA study). *J. Peripher. Nerv. Syst,* 18**,** 130-140.

Levey, A. S., Stevens, L. A., Schmid, C. H., Zhang, Y. L., Castro, A. F., III, Feldman, H. I., Kusek, J. W., Eggers, P., van Lente, F., Greene, T. & Coresh, J. 2009. A new equation to estimate glomerular filtration rate. *Ann. Intern. Med,* 150**,** 604-612.

Lewis, R. A., Cornblath, D. R., Hartung, H. P., Sobue, G., Lawo, J. P., Mielke, O., Durn, B. L., Bril, V., Merkies, I. S. J., Bassett, P., Cleasby, A. & Schaik, I. N. 2020. Placebo effect in chronic inflammatory demyelinating polyneuropathy: The PATH study and a systematic review. *Journal of the Peripheral Nervous System,* 25**,** 230-237.

Markvardsen, L. & Harbo, T. 2017. Subcutaneous immunoglobulin treatment in CIDP and MMN. Efficacy, treatment satisfaction and costs. *Journal of the Neurological Sciences,* 378**,** 19-25.

Markvardsen, L. H., Harbo, T., Sindrup, S. H., Christiansen, I., Andersen, H., Jakobsen, J. & Danish CIDP and MMN Study Group 2014. Subcutaneous immunoglobulin preserves muscle strength in chronic inflammatory demyelinating polyneuropathy. *Eur. J. Neurol,* 21**,** 1465-1470.

Matsui, N. 2012. Multifocal motor neuropathy: current review of epidemiology and treatment. *Rinsho shinkeigaku = Clinical neurology,* 52**,** 920-2.

Mehndiratta, M. M. & Hughes, R. A. 2012. Plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochrane Database Syst. Rev,* 9**,** CD003906.

Merkies, I. S., Schmitz, P. I., Samijn, J. P., Meche, F. G., Toyka, K. V. & van Doorn, P. A. 2000. Assessing grip strength in healthy individuals and patients with immune-mediated polyneuropathies. *Muscle Nerve,* 23**,** 1393-1401.

Merkies, I. S., van Nes, S. I., Hanna, K., Hughes, R. A. & Deng, C. 2010. Confirming the efficacy of intravenous immunoglobulin in CIDP through minimum clinically important differences: shifting from statistical significance to clinical relevance. *J Neurol Neurosurg Psychiatr,* 81**,** 1194-1199.

Misbah, S., Sturzenegger, M. H., Borte, M., Shapiro, R. S., Wasserman, R. L., Berger, M. & Ochs, H. D. 2009. Subcutaneous immunoglobulin: Opportunities and outlook. *Clin Exp Immunol,* 158 Suppl 1**,** 51-59.

Moore, M. L. & Quinn, J. M. 2008. Subcutaneous immunoglobulin replacement therapy for primary antibody deficiency: advancements into the 21st century. *Ann Allergy Asthma Immunol,* 101**,** 114-121.

Nicolay, U., Kiessling, P., Berger, M., Gupta, S., Yel, L., Roifman, C. M., Gardulf, A., Eichmann, F., Haag, S., Massion, C. & Ochs, H. D. 2006. Health-related quality of life and treatment satisfaction in North American patients with primary immunedeficiency diseases receiving subcutaneous IgG self-infusions at home. *J Clin Immunol,* 26**,** 65-72.

Nobile-Orazio, E., Cocito, D., Jann, S., Uncini, A., Beghi, E., Messina, P., Antonini, G., Fazio, R., Gallia, F., Schenone, A., Francia, A., Pareyson, D., Santoro, L., Tamburin, S., Macchia, R., Cavaletti, G., Giannini, F., Sabatelli, M. & IMC Trial Group 2012. Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial. *Lancet Neurol,* 11**,** 493-502.

Ochs, H. D., Gupta, S., Kiessling, P., Nicolay, U., Berger, M. & Group, S. I. S. 2006. Safety and efficacy of self-administered subcutaneous immunoglobulin in patients with primary immunodeficiency diseases. *J Clin Immunol,* 26**,** 265-273.

Orange, J. S., Hossny, E. M., Weiler, C. R., Ballow, M., Berger, M., Bonilla, F. A., Buckley, R., Chinen, J., El-Gamal, Y., Mazer, B. D., Nelson, R. P., Jr., Patel, D. D., Secord, E., Sorensen, R. U., Cunningham-Rundles, C. & Primary Immunodeficiency Committee of American Academy of Allergy, A. a. I. 2006. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol,* 117**,** S525-S553.

Q Core Medical Ltd. 2021. User Manual: Sapphire Multi-therapy & Epidural Infusion Pumps. R15.10 – English – EU.UK and ANZ. [Accessed 27 Mar 2024]: https://eitanmedical.com/user-manual/.

Patwa, H. S., Chaudhry, V., Katzberg, H., Rae-Grant, A. D. & So, Y. T. 2012. Evidence-based guideline: Intravenous immunoglobulin in the treatment of neuromuscular disorders: Report of the therapeutics and technology assessment subcommittee of the American Academy of Neurology. *Neurology,* 78**,** 1009-1015.

Schiff, R., Wasserman, R. L., Stein, M., Melamed, I., Leibl, H., Engl, W. & Yocum, R. 2008. Recombinant human hyaluronidase facilitates dispersion of subcutaneously administered Gammagard Liquid, enabling administration of full monthly dose in single site with improved bioavailability in immunodeficient patients. *Clin Exp Immunol,* 154 Suppl 1**,** 121-122.

Terenghi, F., Cappellari, A., Bersano, A., Carpo, M., Barbieri, S. & Nobile-Orazio, E. 2004. How long is IVIg effective in multifocal motor neuropathy? *Neurology,* 62**,** 666-668.

van Asseldonk, J. T., Franssen, H., van den Berg-Vos, R. M., Wokke, J. H. & van den Berg, L. H. 2005. Multifocal motor neuropathy. *Lancet Neurol,* 4**,** 309-319.

van Nes, S. I., Vanhoutte, E. K., van Doorn, P. A., Hermans, M., Bakkers, M., Kuitwaard, K., Faber, C. G. & Merkies, I. S. J. 2011. Rasch-built Overall Disability Scale (R-ODS) for immune-mediated peripheral neuropathies. *Neurology,* 76**,** 337-345.

van Schaik, I. N., Eftimov, F., van Doorn, P. A., Brusse, E., van den Berg, L. H., Van der Pol, W. L., Faber, C. G., van Oostrom, J. C., Vogels, O. J., Hadden, R. D., Kleine, B. U., van Norden, A. G. W., Verschuuren, J. J. G. M., Dijkgraaf, M. G. W. & Vermeulen, M. 2010. Pulsed high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind, randomised, controlled trial. *Lancet Neurol,* 9**,** 245-253.

van Schaik, I. N., van den Berg, L. H., de Haan, R. & Vermeulen, M. 2005. Intravenous immunoglobulin for multifocal motor neuropathy. *Cochrane Database Syst Rev***,** CD004429.

Vlam, L., Van der Pol, W. L., Cats, E. A., Straver, D. C., Piepers, S., Franssen, H. & van den Berg, L. H. 2012. Multifocal motor neuropathy: Diagnosis, pathogenesis and treatment strategies. *Nat. Rev. Neurol,* 8**,** 48-58.

Wasserman, R. L., Stein, M. R., Melamed, I., Kobrynski, L. J., Gupta, S., Puck, J. M., Rubinstein, A., Engl, W., McCoy, B., Leibl, H. & Yel, L. 2015. Long-term efficacy and safety of recombinant human hyaluronidase (rHuPH20)-facilitated subcutaneous infusion of immnoglobulin G (IgG) (HyQvia; IGHy) in patients with primary immunodeficiencies. *J Allergy Clin Immunol,* 135**,** AB96-AB96.

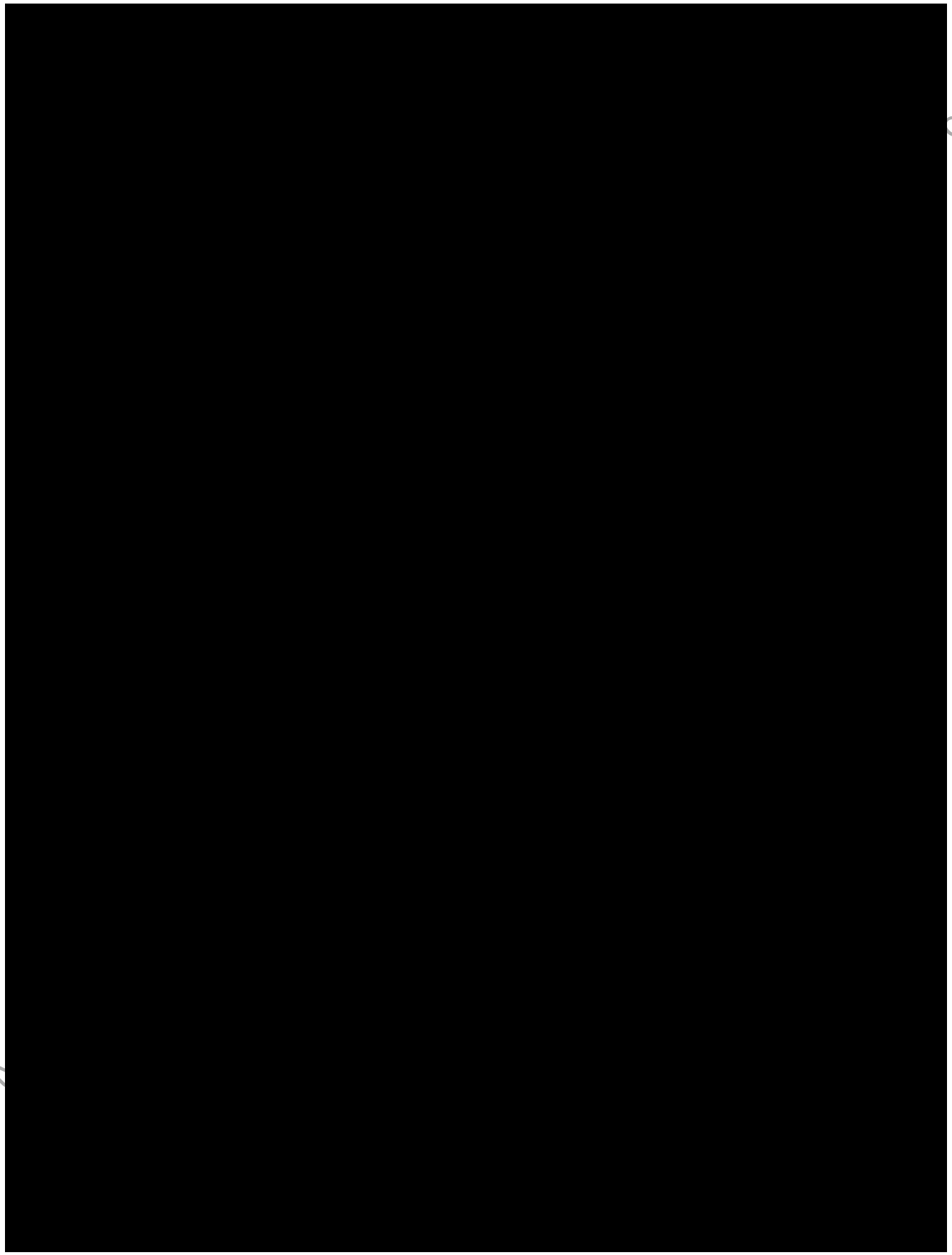
Wiesik-Szewczyk, E., Sołdacki, D., Paczek, L. & Jahnz-Różyk, K. 2020. Facilitated Subcutaneous Immunoglobulin Replacement Therapy in Clinical Practice: A Two Center, Long-Term Retrospective Observation in Adults With Primary Immunodeficiencies. *Frontiers in Immunology,* 11**,** 981.

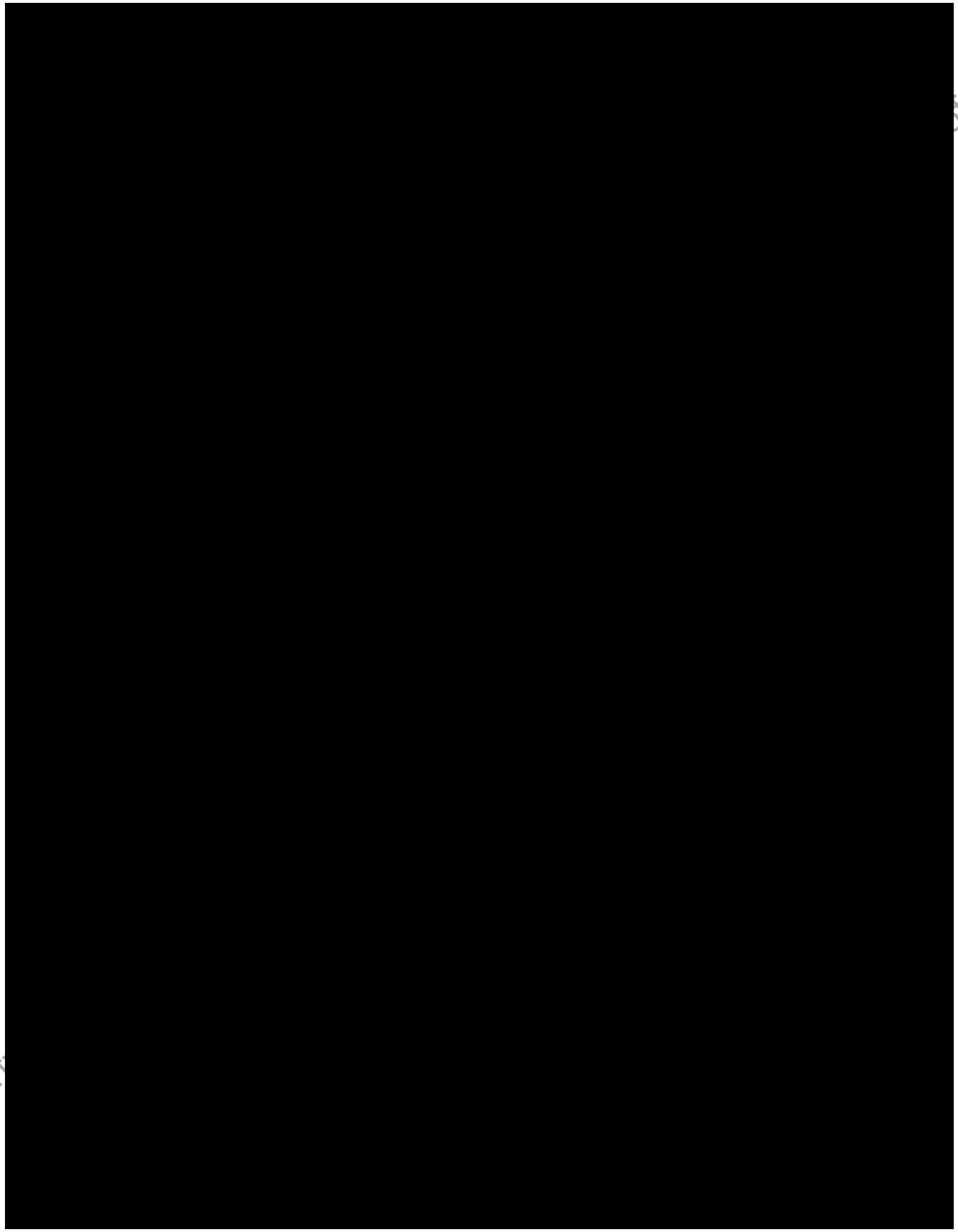
World Health Organization 2003. Toxicity grading scale for determining the severity of adverse events. Section VIII: Appendices Monitoring and Reporting Adverse Events. 2003:132-5.

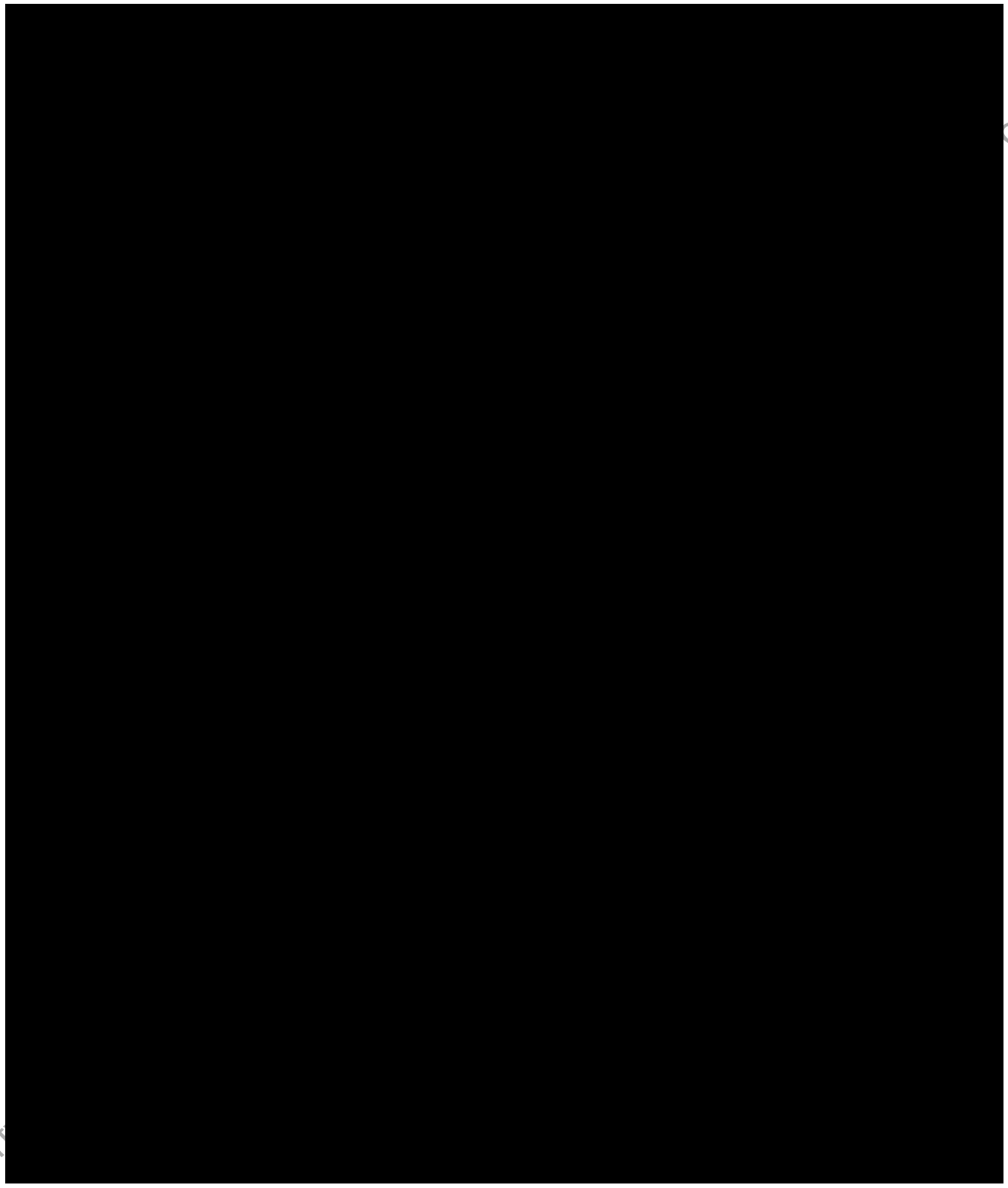
[redacted]

[redacted]

[redacted]







APPENDIX F. PROTOCOL HISTORY

Date	Amendment Number	Region
27 Mar 2024	**Amendment 3**	**Japan**
18 May 2022	Amendment 2	Japan
16 Aug 2021	Amendment 1	Japan
31 Mar 2021	Original	Japan

Changes in Amendment 2

The following is a summary of changes made in the amendment:

- To add a note regarding skin reactions on 14th exclusion criterion in Sections 2 and 7.2.
  Justification: To clarify skin reactions that are not consistent with hypersensitivity reaction following administration of human blood products.
- To add a detailed description to "study termination" for which the administration of TAK-771 can be continued in Sections 2 and 9.3.4.
  Justification: To clarify the timing until when the administration can be continued.
- To revise the description regarding the dosing interval of study drug in Sections 8.1.3 and 9.3.2.
  Justification: To clarify the procedure how investigator will determine the dosing interval of study drug.
- To add infusion pump used for study drug administration as "Device used in clinical trial" in Section 8.2.
  Justification: To add some descriptions in accordance with the revision of Japanese GCP.
- To add the description regarding the delivery of the study drug from the study site to the subject's home in Section 8.4.
  Justification: To maintain subjects' access to the study drug even under unavoidable circumstances such as the COVID-19 pandemic.
- To add a section for reports of product quality complaints in Section 8.5.
  Justification: To clarify the reporting method of the product quality complaints.
- To modify the blood sampling volume for each test and the maximum total blood sampling volume in Section 9.1.9.
  Justification: To clarify the volume in line with the actual blood sampling.
- To correct the description regarding screening period in Section 9.3.1.
  Justification: To clarify the timepoint of screening/baseline visits in screening period.

- To add the description about remote monitoring in Section 14.1.
  Justification: To allow remote monitoring in case alternative approaches are needed for study site monitoring visits.
- To delete explanation of ICF signers if subjects are under the age of 20 in Section 15.2.
  Justification: Eligible subjects are ≥18 years old in this study and adult age was lowered to the age of 18 due to the revision of domestic civil law.
- Addition of the total amount of blood sampling at each visit in tables in Appendix A.
  Justification: To clarify the total amount of blood sampling at each visit.
- To add contact information of Emergency Center for Safety Information in Appendix E.
  Justification: To specify the contact information in the study protocol.
- To add the past change history of protocol as Appendix F.
- Correction of inconsistencies within the protocol and errors.

Changes in Amendment 1

The following is a summary of changes made in the amendment:

- Amendment History and SUMMARY OF CHANGES were added.
- TAK-771 Dose and Dosing Interval in Epoch 1 were added in Section 6.1.
  Justification: To add explanation and tables (Table 6-1 6-2, and Table 6-3) for making better understanding on dose and dosing interval in ramp-up schedule.
- To add description of blood sample volume which will be drawn at each visit in Section 9.1.9.
  Justification: To respond to a request from PMDA
- Description of ECG Procedure was added in Section 9.1.12.
  Justification: to clarify how to interpret the ECG by investigators.
- Description of Treatment Period was added in Section 9.3.2.
  Justification: to add a description that subjects who are well-experienced in self-administration can administer TAK-771 at home, with remote video monitoring by HCPs if needed.
- Description of Final Visit or Early Termination was added in Section 9.3.4.
  Justification: to clarify AE follow up.
- Interim Analysis was added in Section 13.2.
  Justification: to support the Japanese New Drug Application submission.

- To add explanation of ICF signers if subjects are under the age of 20 in Section 15.2.
  Justification: To respond to a request from PMDA.
- Correction of inconsistencies within the protocol amendment 1.