14 December 2023
EMA/CHMP/10327/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

HyQvia

International non-proprietary name: Human normal immunoglobulin

Procedure No. EMEA/H/C/002491/II/0087

Marketing authorisation holder (MAH) Baxalta Innovations GmbH

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ANCOVA	Analysis of covariance
AR	adverse reaction
$AUC_{0\text{-}D8}$	area under the concentration-time curve from time zero (Day 1) to Day 8
AUC_{last}	area under the concentration-time curve from time zero until the last quantifiable concentration
BL	baseline
BMI	Body mass index
BW	Body weight
CCDS	Company Core Data Sheet
CI	confidence interval
CIDP	chronic inflammatory demyelinating polyradiculoneuropathy
cIGSC	Conventional subcutaneous immunoglobulin
CL/F	apparent body clearance
C_{max}	maximum concentration
CSR	clinical study report
DA	demyelinating abnormalities
DL	Dose level
EDX	electrodiagnostic
EFNS	European Federation of Neurological Societies
EMA	European Medicines Agency
EU	European Union
EQ-5D	European Quality of Life – 5 Dimensions
ER	Emergency room
FDA	Food and Drug Administration
HIV	human immunodeficiency virus
IA	Interim analysis
iCSR	interim clinical study report
IgG	immunoglobulin G
IGI	immune globulin infusion (human)
IGIV/IVIg	intravenous immunoglobulin G
IGSC/SCIg	subcutaneous immunoglobulin G
INCAT	Inflammatory Neuropathy Cause and Treatment
IP	Investigational product
ISS	Integrated Summary of Safety
IV	intravenous(ly)
LS	Least square
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
MRC	Medical Research Council
N	number
Nab	neutralizing antibodies
OC	Other concern
PD	Protocol deviations
PID	primary immunodeficiency disease
PK	Pharmacokinetics
PNS	Peripheral Nerve Society
PP set	Per protocol set
PRO	Patient-reported outcome
rHuPH20	recombinant human hyaluronidase PH20
R-ODS	Rasch-built Overall Disability Scale
SAE	Serious adverse event
SAR	Suspected adverse event
SAP	Statistical analysis plan

SAS	Safety analysis set
SC	subcutaneous(ly)
SD	Standard deviation
SF-36	Short Form-36
SOC	System Organ Class
TDL	target dose level
TEAE	treatment-emergent adverse event
$t_{1/2}$	Half-life
t_{max}	time of maximum observed serum concentration
TSQM-9	9-item Treatment Satisfaction Questionnaire for Medication
US	United States
VZ/F	apparent volume of distribution

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Baxalta Innovations GmbH submitted to the European Medicines Agency on 26 January 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) in adults for HyQvia, based on final results from studies 161403 and ABV-771-1001; and interim results from study 161505. 161403 and 161505 are interventional Phase III efficacy and safety studies respectively, while ABV-771-1001 is an interventional Phase I safety study. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 14.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 14 November 2019 (EMA/CHMP/SAWP/600210/2019), 22 January 2015 (EMA/CHMP/SAWP/51311/2015) and 20 May 2010 (EMA/CHMP/SAWP/287086/2010). The Scientific Advice pertained to clinical aspects of the dossier (see section 2.1.3).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jan Mueller-Berghaus Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	26 January 2023
Start of procedure:	25 February 2023
CHMP Rapporteur Assessment Report	24 April 2023
PRAC Rapporteur Assessment Report	27 April 2023
PRAC members comments	3 May 2023
Updated PRAC Rapporteur Assessment Report	17 May 2023
PRAC Outcome	12 May 2023
CHMP members comments	15 May 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 May 2023
Request for supplementary information (RSI)	25 May 2023
CHMP Rapporteur Assessment Report	14 August 2023
PRAC Rapporteur Assessment Report	16 August 2023
PRAC members comments	29 August 2023
Updated PRAC Rapporteur Assessment Report	31 August 2023
PRAC Outcome	31 August 2023
CHMP members comments	4 September 2023
Updated CHMP Rapporteur Assessment Report	7 September 2023
Request for supplementary information (RSI)	14 September 2023
CHMP Rapporteur Assessment Report	15 November 2023
PRAC Rapporteur Assessment Report	17 November 2023
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	23 November 2023
PRAC Outcome	30 November 2023
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	6 December 2023 8 December 2023
CHMP Opinion	14 December 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Chronic inflammatory demyelinating polyneuropathy *(*CIDP) is a chronic acquired immune-mediated peripheral neuropathy that, in its most common form, presents as a symmetric, proximal, and distal demyelinating peripheral neuropathy where motor loss is greater than sensory loss. The clinical course may be slowly progressive over at least 8 weeks and/or follow a relapsing-remitting course. Deep tendon reflexes are diminished or absent. Sensory symptoms include numbness, tingling, and painful paresthesias. Cranial nerve involvement is less commonly seen. Balance can be impaired due to loss of proprioception.

The therapeutic indication initially claimed by the MAH was:

Immunomodulatory therapy in adults:

For the treatment of patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy

Epidemiology and risk factors

The 2021 European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) guidelines require electrodiagnostic testing with findings consistent with demyelination for a diagnosis of CIDP (Koller et al., 2005, Patwa et al., 2012, Van den Bergh et al., 2021). Worldwide estimates of the prevalence of CIDP range from 1.9 to 8.9 per 100,000 with an annual incidence of 0.15 to 1.6 per 100,000 (Broers et al., 2019, Iijima et al., 2008, Laughlin et al., 2009, Lunn et al., 1999, McLeod et al., 1999, Mygland and Monstad, 2001). The peak incidence is between the ages of 30 to 60 years (Dalakas, 2011). Epidemiological studies show a male predominance with both incidence and prevalence increasing with age (Broers et al., 2019). There are no known risk factors (Broers et al., 2019). CIDP is a clinically and immunologically heterogeneous disease. Approximately 60% of patients may have a chronic progressive disease course (± remissions and relapses) and are usually older, whereas about 30% may follow a mostly relapsing-remitting course and tend to be younger.

Aetiology and pathogenesis

Although the exact aetiology is unknown, CIDP is considered an immune-mediated disorder characterized by inflammatory changes and infiltration of macrophages and T-cells in the myelin sheath of the nerves. Chronic inflammation results in demyelination, remyelination, and onion bulb formation. Long-term demyelination leads to axonal loss. The amount of axonal loss determines the level of disability and long-term prognosis (Koller et al., 2005, Ulane and Brannagan, 2012).

Clinical presentation, diagnosis

CIDP puts a significant burden on patients, their families, and society. CIDP causes gait disturbance and weakness resulting in impaired dexterity in carrying out daily tasks (Querol et al., 2021). Paresthesias can result in painful symptoms such as aching, jabbing, searing pain, or burning pain (Ulane and Brannagan, 2012). Up to one-third of patients with CIDP retire early due to weakness, pain, and chronic fatigue. Additionally, employment and leisure activities can be affected resulting in economic hardships due to lost wages, unemployment, and disruption of family life (Querol et al., 2021). Disability from this disease may persist for years or even decades with the need for ongoing treatment (Oaklander et al., 2017).

Management

The 2021 EFNS/PNS guidelines for CIDP recommend intravenous (IV) immunoglobulin G (IVIg) or corticosteroids as first-line treatments (Van den Bergh et al., 2021). IVIg is an effective treatment for CIDP and is used for both induction and maintenance purposes (Eftimov et al., 2013, Harbo et al., 2009, Hughes et al., 2001, Hughes et al., 2008, Kuitwaard et al., 2010, Léger et al., 2013, Mendell et al., 2001, Nobile-Orazio et al., 2012, Patwa et al., 2012, van Schaik et al., 2002). The guidelines also strongly recommend using subcutaneous (SC) immunoglobulin G (SCIg) for maintenance treatment in CIDP with no preference for either IVIg or SCIg.

The therapeutic efficacy of SCIg as a maintenance treatment in patients with CIDP is well established (Cocito et al., 2014, Cocito et al., 2011, Köller et al., 2006, Lee et al., 2008, Markvardsen et al., 2013, van Schaik et al., 2018).

2.1.2. About the product

HyQvia is a subcutaneous (SC) immune globulin infusion (IGI) 10% (human) with recombinant human hyaluronidase (rHuPH20). This combination is marketed as HyQvia in the European Union (EU). It is approved as replacement therapy in adults, children and adolescents (0 to 18 years) in primary immunodeficiency syndromes with impaired antibody production, secondary immunodeficiencies in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure or serum immunoglobulin G (IgG) level of <4 g/L (HyQvia SmpC).

The rHuPH20 component of HyQvia increases permeability of the SC tissue by temporarily depolymerizing hyaluronan. In the doses administered, rHuPH20 of HyQvia acts locally. The effects of the hyaluronidase are reversible, and permeability of the SC tissue is restored within 24 to 48 hours.

The IGI 10% of HyQvia supplies a broad spectrum of opsonizing and neutralizing immunoglobulin G (IgG) antibodies against infectious agents. Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled human plasma from not fewer than 1000 donations. It has a distribution of IgG subclasses closely proportional to that in native human plasma. Adequate doses of human normal immunoglobulin may restore abnormally low IgG levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated but includes immunomodulatory effects.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The clinical development program of HyQvia for CIDP included the following 3 studies:

- The efficacy, safety, and tolerability of HyQvia were investigated in 1 pivotal clinical study in adult subjects with CIDP (Study 161403). Completed.
- Long-term tolerability and safety of HyQvia were assessed in an extension study (Study 161505) in subjects who completed the pivotal trial (Study 161403). Only interim results available.
- The tolerability, safety, and pharmacokinetics of HyQvia with ramp-up and no ramp-up dosing were evaluated in healthy adult subjects (Study TAK-771-1001). Completed.

Scientific advice

Since 2010, the MAH´s pursuit of the CIDP indication in the EU has resulted in three different interactions with EMA via Scientific Advices: in 2010 (EMA/CHMP/SAWP/287091/2010), 2015 (EMA/CHMP/SAWP/51311/2015) and 2019 (EMA/CHMP/SAWP/600210/2019).

The first two Scientific Advices (2010 and 2015) focused mainly on the design of planned Phase 3 pivotal studies for both Kiovig (2010, regarding study 160901) and Kiovig/HyQvia (2015, regarding study

161403) in order to pursue the CIDP indication. CHMP generally agreed on the proposed study design, endpoints, study population and study assessments.

Regarding the latest Scientific Advice from 2019, the MAH requested feed-back on applying for the indication with a minimum of 30 patients from 161403 with an interim safety report plus a literature review, while proposing to deliver the final results upon study completion. EMA´s recommendation was to deliver a completed Phase III study including results from the primary endpoint. With the current approach, the MAH is fulfilling EMA´s request by providing proof of efficacy and safety with the completed study 161403 including 132 dosed patients.

2.1.4. General comments on compliance with GCP

All studies with HyQvia in CIDP were conducted in compliance with Good Clinical Practice principles set forth in Title 21 of the US Code of Federal Regulations, parts 50, 54, 56, 312, and 314, International Conference on Harmonisation Guidelines for Good Clinical Practice, European Commission Directive 2005/28/EC, and local and national regulatory requirements. There was a compliance issue in the Phase 1 study in healthy subjects (TAK-771-1001), but this issue had no impact on subject safety and data reliability.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

According to the current CHMP guideline on environmental risk assessment (CHMP/SWP/4447/00 corr 2), for products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment. As HyQvia contains a naturally occurring protein as active pharmaceutical ingredient, HyQvia falls within the scope of this provision. The MAH's ERA, providing a justification for not performing a detailed environmental risk assessment for HyQvia, is thereby considered acceptable.

2.2.2. Conclusion on the non-clinical aspects

From the non-clinical point of view, the extension of indication application is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study	Study Identifier	Objective (of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and safety	161403	To evaluate the efficacy of HyQvia as a maintenance therapy for CIDP to prevent relapse of neuromuscular disability and impairment.	Phase 3, double-blind, placebo-controlled, multi-centre study	Epoch 1: (Active Treatment) Sequential SC administration of rHuPH20 solution followed by IGI, 10%. Every 2, 3, or 4 weeks, except during the ramp-up period. (Placebo treatment) Sequential SC administration of rHuPH20 solution followed by 0.25% human albumin in LR solution, every 2, 3, or 4 weeks, except during the ramp-up period.	132 dosed with IP	Subjects ≥18 years with documented diagnosis of definite or probable CIDP, currently on stable doses of IVIg treatment	Epoch 1: SC treatment period of 6 months	Completed, full CSR
Safety and efficacy	161505	To evaluate the long- term safety, tolerability, and immunogenicity of HyQvia	Phase 3b, open-label, non-controlled, multi-centre study	Subjects continue to receive the same dose and dosing regimen of HyQvia in the Extension Study as the subject's full dose received in Epoch 1 of the Phase 3 Study 161403 (Sequential SC administration of rHuPH20 solution followed by IGI, 10%)	Ongoing. Approx-imately 88 subjects	Subjects with CIDP ≥18 years who have rolled over from Study 161403	Each subject had the opportunity to receive HyQvia until approval of HyQvia marketing authorization for the treatment of CIDP in either US or EU (whichever comes later)	Ongoing, Interim CSR
Tolerability, safety, and PK	TAK-771-1001	Primary: To assess the tolerability of HyQvia with and without ramp-up dosing in healthy adult subjects. Secondary: To assess the safety and immunogenicity of HYQVIA with and without ramp-up dosing in healthy adult subjects. To characterize the pharmacokineti	Phase 1, open-label, non-controlled, single centre study	Study Parts 1 & 2: the target dose level (TDL) was 0.4 g/kg for Part 1 and 1.0 g/kg for Part 2, achieved through dose ramp-up or no ramp up. Each study part consisted of three Treatment Arms (Part 1: Treatment Arms 1-3 and Part 2: Treatment Arms 4-6): • Treatment Arms 1 and 4	51 total male and female	Healthy subjects	8 weeks for Treatment Arms 1 and 4; 9 weeks for Treatment Arms 2, 3, 5, and 6	Completed, full CSR

		cs (PK) of total IgG and IgG subclasses after subcutaneous administration of HyQvia in healthy adult subjects.		followed ramp up Schedule-A, in which subjects received HyQvia from ¼ of the TDL at Week 1 to the full TDL at Week 8. • Treatments Arms 2 and 5 followed ramp up Schedule-B, in which subjects received HyQvia from ½ of the TDL at Week 1 to the full TDL at Week 5. • Treatment Arms 3 and 6 followed ramp up Schedule-C, in which subjects received the full TDL at Week 1 without ramp-up dosing.				

2.3.2. Pharmacokinetics

The clinical pharmacology of HyQvia has been evaluated in Study TAK-771-1001, in healthy adults, and in Study 161403, in adults diagnosed with CIDP.

Study TAK-771-1001

This was a Phase 1 study to evaluate the tolerability, safety, and immunogenicity of HyQvia with and without ramp-up dosing and to characterize the PK of total IgG and IgG subclasses in serum after SC administration of HyQvia in healthy adults.

The study was conducted in 2 parts with a target dose level (TDL) of either 0.4 g/kg (Part 1) or 1.0 g/kg (Part 2) and administered in a dose ramp-up or no ramp-up (ie, direct administration of the TDL) manner. Each study part consisted of 3 treatment arms (Part 1: Treatment Arms 1 through 3 and Part 2: Treatment Arms 4 through 6), as follows:

- Treatment Arms 1 and 4 followed Ramp-Up Schedule-A (Sch-A), in which subjects received HyQvia from 1/4 of the TDL at Week 1 to the full TDL at Week 8.
- Treatment Arms 2 and 5 followed Ramp-Up Schedule-B (Sch-B), in which subjects received HyQvia from 1/2 of the TDL at Week 1 to the full TDL at Week 5.
- Treatment Arms 3 and 6 followed Ramp-Up Schedule-C (Sch-C), in which subjects directly received the full TDL at Week 1 without Ramp-Up dosing.

The planned dose levels including ramp-up dose levels of IGI, 10% that were evaluated in this study are outlined in **Table 1**.

Table 1. Dose Levels (DL) on Study Day 1 for Single-Dose Pharmacokinetic Assessment

DL	Fraction of TDL	Part 1 (g/kg)	Part 2 (g/kg)
DL1	1/4 of TDL	0.1	0.25
DL2	1/2 of TDL	0.2	0.5
DL3	3/4 of TDL	0.3	0.75
DL4	TDL	0.4	1.0

Subjects who met all eligibility criteria were assigned to the 3 treatment arms in each study part at an allocation ratio of 1:1:1, and a minimum of 3 subjects were included in each of the 2-body mass index (BMI) groups (18 to <25 kg/m2 and ≥25 to 30 kg/m2) in each treatment arm, which was achieved using stratified allocation (BMI was the stratification factor). Each subject participated in only 1 treatment arm.

Subjects Disposition

Table 2 Disposition by Treatment Arm (Enrolled Set) Overall

	Ramp-Up Schedule A		Ramp-Up Schedule B		Ramp-Up	No Ramp-Up Schedule C		No Ramp-Up	
	Low TDL (TA 1) (N=8)	High TDL (TA 4) (N=8)	Low TDL (TA 2) (N=8)	High TDL (TA 5) (N=9)	Total (N=33)	Low TDL (TA 3) (N=8)	High TDL (TA 6) (N=10)	Total (N=18)	Overall Total (N=51)
Safety Set	8 (100.0)	8 (100.0)	8 (100.0)	9 (100.0)	33 (100.0)	8 (100.0)	10 (100.0)	18 (100.0)	51 (100.0)
Pharmacokinetic Set	8 (100.0)	8 (100.0)	8 (100.0)	9 (100.0)	33 (100.0)	8 (100.0)	10 (100.0)	18 (100.0)	51 (100.0)
Reason for Exclusion from PK Set									
Subject was not in the safety analysis population	0	0	0	0	0	0	0	0	0
Subject did not have any evaluable post-dose serum concentration for total IgG or IgG subclasses	0	0	0	0	0	0	0	0	0
Completed Study	6 (75.0)	8 (100.0)	8 (100.0)	7 (77.8)	29 (87.9)	6 (75.0)	3 (30.0)	9 (50.0)	38 (74.5)
Discontinued Study	2 (25.0)	0	0	2 (22.2)	4 (12.1)	2 (25.0)	7 (70.0)	9 (50.0)	13 (25.5)
Primary Reason for Discontinuation									
Adverse Event	0	-	-	0	0	0	0	0	0
Death	0	-	-	0	0	0	0	0	0
Lost to Follow-up	1 (12.5)	-	-	1 (11.1)	2 (6.1)	0	2 (20.0)	2 (11.1)	4 (7.8)
Non-Compliance with Study Drug	0	-	-	0	0	0	0	0	0
Non-Compliance with Study Procedures	0	-	-	0	0	1 (12.5)	0	1 (5.6)	1 (2.0)
Physician Decision	0	-	-	0	0	0	0	0	0
Pregnancy	1 (12.5)	-	-	0	1 (3.0)	0	0	0	1 (2.0)
Protocol Deviation	0	-	-	0	0	0	0	0	0
Site Terminated by Sponsor	0	-	-	0	0	0	0	0	0
Study Terminated by Sponsor	0	-	-	0	0	0	0	0	0
Withdrawal by Subject	0	-	-	1 (11.1)	1 (3.0)	1 (12.5)	5 (50.0)	6 (33.3)	7 (13.7)
Other	0	-	-	0	0	0	0	0	0

A total of 51 subjects were enrolled in the study, 33 subjects into the Ramp-Up dosing group (Treatment Arms 1, 2, 4, and 5) and 18 subjects into the No Ramp-Up dosing group (Treatment Arms 3 and 6). A minimum of 3 subjects were included in each of the two BMI groups (18 to <25 kg/m2 and ≥25 to 30 kg/m2) in each treatment arm.

A total of 38 (74.5%) subjects completed the study, and 13 (25.5%) subjects discontinued the study. The number of subjects who discontinued the study in the No Ramp-Up dosing group was higher (9/18 [50%] subjects) compared to the Ramp-Up dosing groups (4/33 [12.1%] subjects). Withdrawal by subject was the common reason for early discontinuation (n=7), followed by lost to follow-up (n=4).

Protocol deviation

Per protocol, treatment arms would need to be initiated in parallel in each study part, and subjects would be assigned to the 3 treatment arms in each study part at a randomisation ratio of 1:1:1, using stratified randomisation where the 2 BMI groups (18 to <25 kg/m2 and ≥25 to 30 kg/m2) were the strata. However, as agreed with the Sponsor, subjects who met eligibility criteria were assigned to 1 of the treatment arms in each study part, in sequence to allow completion of treatment arms sequentially, instead of in parallel, though the stratification based on BMI groups did still occur. Thus, randomisation did not occur as planned in protocol and was captured as significant protocol deviation. All 51 subjects were reported with this deviation.

13 (25.5%) subjects had significant deviations of missing endpoint assessments.

Demographic and Baseline Characteristics

Overall, the mean (SD) age for this study was 35.1 (8.28) years (range: 20 to 50 years). The majority of subjects were White (34 [66.7%] subjects) and of Hispanic or Latino ethnicity (47 [92.2%] subjects). In total, 29 (56.9%) females and 22 (43.1%) males were enrolled in the study (in the low TDL Ramp-Up dosing group [Sch-A], there were a greater number of female subjects [7 {87.5%} subjects] compared to male subjects [1 {12.5%} subject]), and the mean BMI (SD) was 25.51 (3.067) kg/m2.

Table 3 Demographic Characteristics by treatment arm (Safety Set and PK Set)

	Ramp-Up Schedule A		Ramp-Up Schedule B		Ramp-Up	No Ramp-Up Schedule C		No Ramp-Up	
Characteristic	Low TDL (TA 1) (N=8)	High TDL (TA 4) (N=8)	Low TDL (TA 2) (N=8)	High TDL (TA 5) (N=9)	Total (N=33)	Low TDL (TA 3) (N=8)	High TDL (TA 6) (N=10)	Total (N=18)	Overall Total (N=51)
Age (years)[a]									
n	8	8	8	9	33	8	10	18	51
Mean (SD)	28.9 (8.04)	34.4 (6.44)	40.4 (5.01)	36.4 (7.88)	35.1 (7.84)	36.8 (8.58)	34.0 (10.07)	35.2 (9.27)	35.1 (8.28)
Median	27.5	34.5	41.0	34.0	34.0	36.0	34.0	36.0	34.0
Min, Max	20, 41	22, 46	34, 46	27, 49	20, 49	27, 49	23, 50	23, 50	20, 50
Sex [n (%)]									
Male	1 (12.5)	3 (37.5)	4 (50.0)	4 (44.4)	12 (36.4)	4 (50.0)	6 (60.0)	10 (55.6)	22 (43.1)
Female	7 (87.5)	5 (62.5)	4 (50.0)	5 (55.6)	21 (63.6)	4 (50.0)	4 (40.0)	8 (44.4)	29 (56.9)
Ethnicity [n (%)]									
Hispanic or Latino	8 (100.0)	8 (100.0)	6 (75.0)	9 (100.0)	31 (93.9)	6 (75.0)	10 (100.0)	16 (88.9)	47 (92.2)
Not Hispanic or Latino	0	0	2 (25.0)	0	2 (6.1)	2 (25.0)	0	2 (11.1)	4 (7.8)
Not Reported	0	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0	0
Race [n (%)]									
American Indian or Alaska Native	0	0	0	0	0	0	0	0	0
Asian	0	0	0	0	0	0	0	0	0
Black or African American	4 (50.0)	2 (25.0)	4 (50.0)	3 (33.3)	13 (39.4)	2 (25.0)	2 (20.0)	4 (22.2)	17 (33.3)
White	4 (50.0)	6 (75.0)	4 (50.0)	6 (66.7)	20 (60.6)	6 (75.0)	8 (80.0)	14 (77.8)	34 (66.7)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0
Not Reported	0	0	0	0	0	0	0	0	0

Table 4 Demographic Characteristics by treatment arm (Safety Set and PK Set) – continuation

Characteristic	Ramp-Up Schedule A Low TDL (TA 1) (N=8)	Ramp-Up Schedule A High TDL (TA 4) (N=8)	Ramp-Up Schedule B Low TDL (TA 2) (N=8)	Ramp-Up Schedule B High TDL (TA 5) (N=9)	Ramp-Up Total (N=33)	No Ramp-Up Low TDL (TA 3) (N=8)	No Ramp-Up Schedule C High TDL (TA 6) (N=10)	No Ramp-Up Total (N=18)	Overall Total (N=51)
Weight (kg) [a]									
n	8	8	8	9	33	8	10	18	51
Mean (SD)	72.74 (5.987)	67.28 (15.941)	71.90 (12.088)	71.66 (10.311)	70.92 (11.248)	71.41 (9.945)	66.61 (7.189)	68.74 (8.609)	70.15 (10.357)
Median	72.65	62.95	71.50	67.00	70.00	71.50	65.30	69.30	70.00
Min, Max	63.0, 80.0	51.0, 98.4	54.4, 97.9	62.4, 91.0	51.0, 98.4	53.4, 83.5	56.0, 77.3	53.4, 83.5	51.0, 98.4
Height (cm) [a]									
n	8	8	8	9	33	8	10	18	51
Mean (SD)	168.24 (3.964)	165.63 (9.757)	167.38 (8.782)	166.66 (7.230)	166.96 (7.425)	165.79 (12.068)	162.15 (9.824)	163.77 (10.701)	165.84 (8.752)
Median	167.65	160.75	166.00	169.50	166.00	162.50	163.25	163.25	166.00
Min, Max	164.0, 175.6	156.0, 182.0	157.0, 181.0	155.0, 175.5	155.0, 182.0	154.0, 186.5	148.0, 173.0	148.0, 186.5	148.0, 186.5
BMI (kg/m^2) [a, b]									
n	8	8	8	9	33	8	10	18	51
Mean (SD)	25.76 (2.664)	24.40 (4.342)	25.58 (2.773)	25.78 (2.944)	25.39 (3.140)	26.08 (3.422)	25.44 (2.789)	25.72 (3.008)	25.51 (3.067)
Median	25.75	25.55	25.95	25.40	25.80	26.60	25.40	25.65	25.80
Min, Max	22.0, 29.4	18.6, 29.7	22.1, 29.9	21.7, 29.9	18.6, 29.9	21.7, 29.9	20.8, 29.1	20.8, 29.9	18.6, 29.9
BMI Category [n (%)]									
18 to < 25 kg/m2	4 (50.0)	4 (50.0)	3 (37.5)	4 (44.4)	15 (45.5)	3 (37.5)	4 (40.0)	7 (38.9)	22 (43.1)
>= 25 to 30 kg/m2	4 (50.0)	4 (50.0)	5 (62.5)	5 (55.6)	18 (54.5)	5 (62.5)	6 (60.0)	11 (61.1)	29 (56.9)

Total IgG Pharmacokinetics Summary

The PK of total IgG and IgG subclasses in serum were characterized based on serum concentration-time profiles after the first infusion (ie, Week 1 dosing). Pharmacokinetic parameters were determined from the IgG (total and subclasses) uncorrected and baseline-corrected serum concentration-time data using non-compartmental analysis based on actual sampling times. No PK parameters were calculated for subjects with 2 or fewer consecutive time points with measurable concentrations.

IgG subclass data were not available at the time of the study report and are not included in this summary. The primary objective of this study was to assess the tolerability of ramp-up vs no ramp-up dosing. The absence of subclass data is not expected to change the primary conclusion of the study, and the subclass data are not considered to have impact on the overall PK conclusions for CIDP.

Parameter

C_{max} maximum observed concentration

t_{max} time of maximum observed serum concentration

AUC_{last} area under the concentration-time curve from time zero to the last quantifiable concentration, calculated using the linear-up/log-down trapezoidal rule.

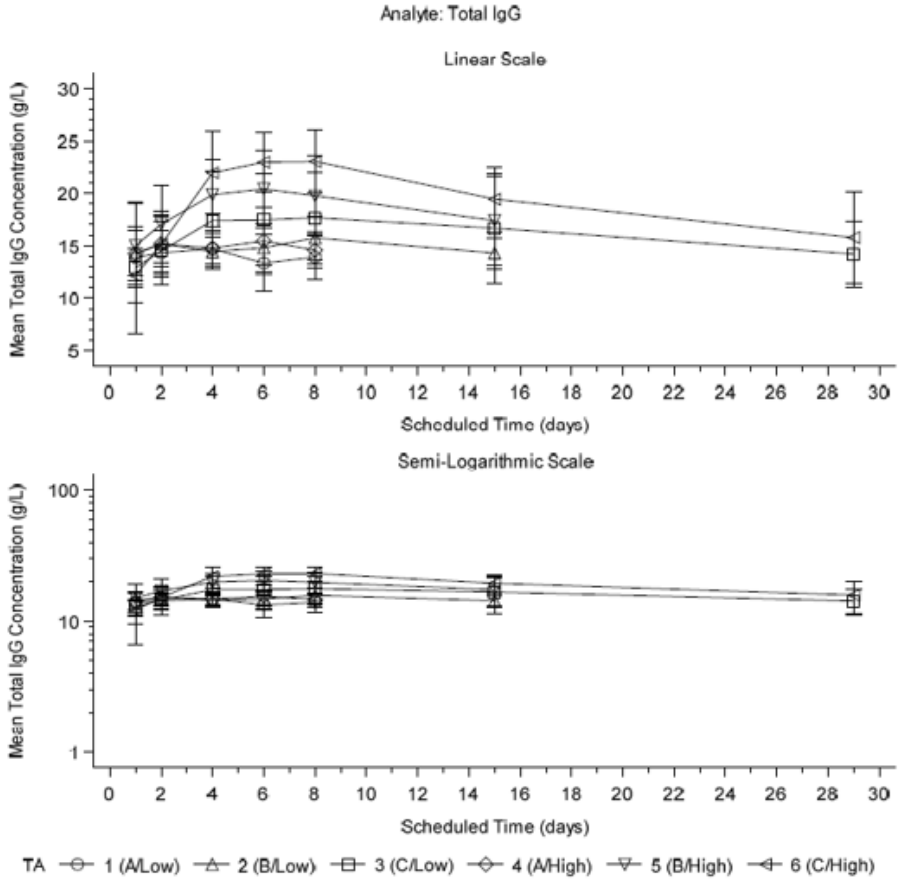
In this method, the linear trapezoidal method of calculation was used for each incremental trapezoid and the log trapezoidal rule for each decremental trapezoid.

AUC_{0-D8} area under the concentration-time curve from time zero (Day 1) to Day 8

Baseline-uncorrected Total IgG Concentrations and PK Parameters

Mean (± standard deviation [SD]) serum baseline-uncorrected concentrations of total IgG vs scheduled time following SC administration of IGI, 10% with rHuPH20 to healthy adult subjects are presented by treatment arm in **Figure 1**.

Figure 1 Mean (±SD) Baseline-Uncorrected IgG Serum concentrations (g/L) vs Time by Treatment Arm on a Linear and Semi-Logarithmic Scale



IgG=immunoglobulin G; SD=standard deviation
Legend indicates treatment schedule in the following way Treatment Arm ([TA] Schedule/Target Dose Level).

Following SC administration of IGI, 10% with rHuPH20 to healthy subjects, mean baseline-uncorrected total IgG concentrations increased with time reaching a peak between 4 to 8 days post dosing and subsequently decreased, not fully reaching baseline levels at the end of the sampling period (Day 8 for Sch-A, Day 15 for Sch-B, and Day 29 for Sch-C). The highest uncorrected total IgG level is observed for Treatment Arm 6 (sampling Sch-C, high TDL) followed by Treatment Arm 5 (sampling Sch-B, high TDL).

Mean baseline-uncorrected values on Day 1 prior to the first dose administration ranged from 12.14 g/L to 15.00 g/L across all treatment arms. Mean baseline-uncorrected concentrations for Treatment Arm 3 (Sch-C, low TDL) and Treatment Arm 6 (Sch-C, high TDL) on Day 1 were 12.89 g/L and 12.14 g/L, respectively.

Serum baseline-uncorrected total IgG PK parameters following SC administration of IGI, 10% with rHuPH20 to healthy adult subjects are summarized by treatment arm in **Table 5**. For all subjects the terminal phase of total IgG could not be adequately estimated due to insufficient data to determine a reliable linear regression of the log concentration vs linear time profile. Considering that limited number of data points following maximum observed concentration (Cmax) were available to generate a reliable log-linear regression, some PK parameters could not be estimated, including area under the curve from time zero extrapolated to infinity (AUC0-inf), terminal disposition elimination rate constant (λz), half-life (t1/2), apparent body clearance (CL/F), and apparent volume of distribution (VZ/F).

Table 5 Summary of Baseline-uncorrected Total IgG Serum Pharmacokinetic Parameters by Treatment Arm (Pharmacokinetic Set)

PK parameter (unit) Dose on Day 1	TA 1, Schedule A, Low TDL (N=8) ¼ of TDL (0.1 g/kg)	TA 2, Schedule B Low TDL (N=8) ½ of TDL (0.2 g/kg)	TA 3, Schedule C Low TDL (N=8) Full TDL (0.4 g/kg)	TA 4, Schedule A High TDL (N=8) ¼ of TDL (0.25 g/kg)	TA 5, Schedule B High TDL (N=9) ½ of TDL (0.5 g/kg)	TA 6, Schedule C High TDL (N=10) Full TDL (1.0 g/kg)
C_{max} (g/L)						
n	7	8	8	8	9	10
Geometric mean	15.36	16.64	18.10	17.16	20.83	24.86
GM 95% CI	13.94, 16.92	14.65, 18.91	15.04, 21.79	14.88, 19.80	18.27, 23.75	22.72, 27.20
GM %CV	10.5	15.4	22.4	17.2	17.2	12.6
t_{max} (day)						
n	7	8	8	8	9	10
Median	4.0	6.0	5.0	3.0	6.0	6.0
Min, max	1.0, 8.0	1.0, 16.0	4.0, 15.0	1.0, 8.0	4.0, 16.1	4.0, 8.0
$AUC_{0\text{-}D8}$ (day*g/L)						
n	7	8	8	8	9	10
Geometric mean	97.48	103.46	112.73	104.00	131.49	140.84
GM 95% CI	85.41, 111.26	94.08, 113.78	93.00, 136.64	93.25, 115.99	114.37, 151.17	130.18, 152.38
GM %CV	14.4	11.4	23.3	13.1	18.3	11.0
AUC_{last} (day*g/L)						
n	7	8	8	8	9	10
Geometric mean	104.28	222.36	378.57	111.07	263.75	324.75
GM 95% CI	91.37, 119.01	203.87, 242.52	249.47, 574.48	99.77, 123.65	208.09, 334.31	227.13, 464.33
GM %CV	14.4	10.4	53.2	12.9	31.6	53.3

$AUC_{0\text{-}D8}$=area under the concentration-time curve from time zero (Day 1) to Day 8. AUC_{last}=area under the curve from the time of dosing to the last measurable concentration; C_{max}=maximum concentration; GM CV%=coefficient of variation of geometric mean; GM 95% CI=geometric mean 95% confidence interval; max=maximum; min=minimum; N=number of subjects in the group; n=number of subjects with reported value; PK=pharmacokinetic; t_{max}=time of maximum observed concentration; TA=treatment arm; TDL=target dose level
Low TDL: 0.4 g/kg (Study Part 1); High TDL: 1.0 g/kg (Study Part 2)
TA 1 (Low TDL) & 4 (High TDL): Schedule A, 1/4 TDL (Days 1, 8), 1/2 TDL (Day 15), 3/4 TDL (Day 29), 1/1 TDL (Day 50).
TA 2 (Low TDL) & 5 (High TDL): Schedule B, 1/2 TDL (Day 1, Day 15), 1/1 TDL (Day 29, Day 57).
TA 3 (Low TDL) & 6 (High TDL): Schedule C, 1/1 TDL Day 1, Day 29 and Day 57.

The geometric mean of the peak total IgG concentration (Cmax) increased with the dose administered on Day 1. The highest Cmax geometric mean of 24.86 g/L was observed for the high TDL of Sch-C, consistent with the highest Day 1 dose being administered in this treatment arm. For other treatment arms the geometric mean Cmax ranged from 15.36 g/L to 20.83 g/L. An increase by 2.5-fold in dose administered on Day 1 (low TDL compared to high TDL) led to an increase in geometric mean of Cmax by 1.12-, 1.25-, and 1.37-fold for Schedules A, B, and C, respectively. Inter-subject variability was low to moderate with geometric mean %CV values ranging from 10.5% to 22.4% (**Table 5**).

Median time to reach Cmax (tmax) ranged from 3.0 to 6.0 days post dose, with individual values ranging from 1.0 to 16.1 days post dose (**Table 5**).

The area under the concentration-time curve from time zero (Day 1) to Day 8 (AUC0-D8) was highest for the high TDL of Sch-B and Sch-C, with geometric mean AUC0-D8 of 131.49 day*g/L and 140.84 day*g/L, respectively. Geometric mean AUC0-D8 results observed within Treatment Arms 1 to 4 were similar, with values ranging from 97.48 day*g/L to 112.73 day*g/L. In general, an increase of the administered dose

on Day 1 did not correspond to the same level of increase in AUC0-D8. An increase by 2.5-fold in dose administered on Day 1 (low TDL compared to high TDL) led to an increase in geometric mean of AUC0-D8 by 1.07-, 1.27-, and 1.25-fold for Schedules A, B, and C, respectively. Inter-subject variability was low to moderate across all treatment arms, with the highest geometric mean %CV being observed for Treatment Arm 3 (Sch-C, low TDL) at 23.3% (**Table 5**).

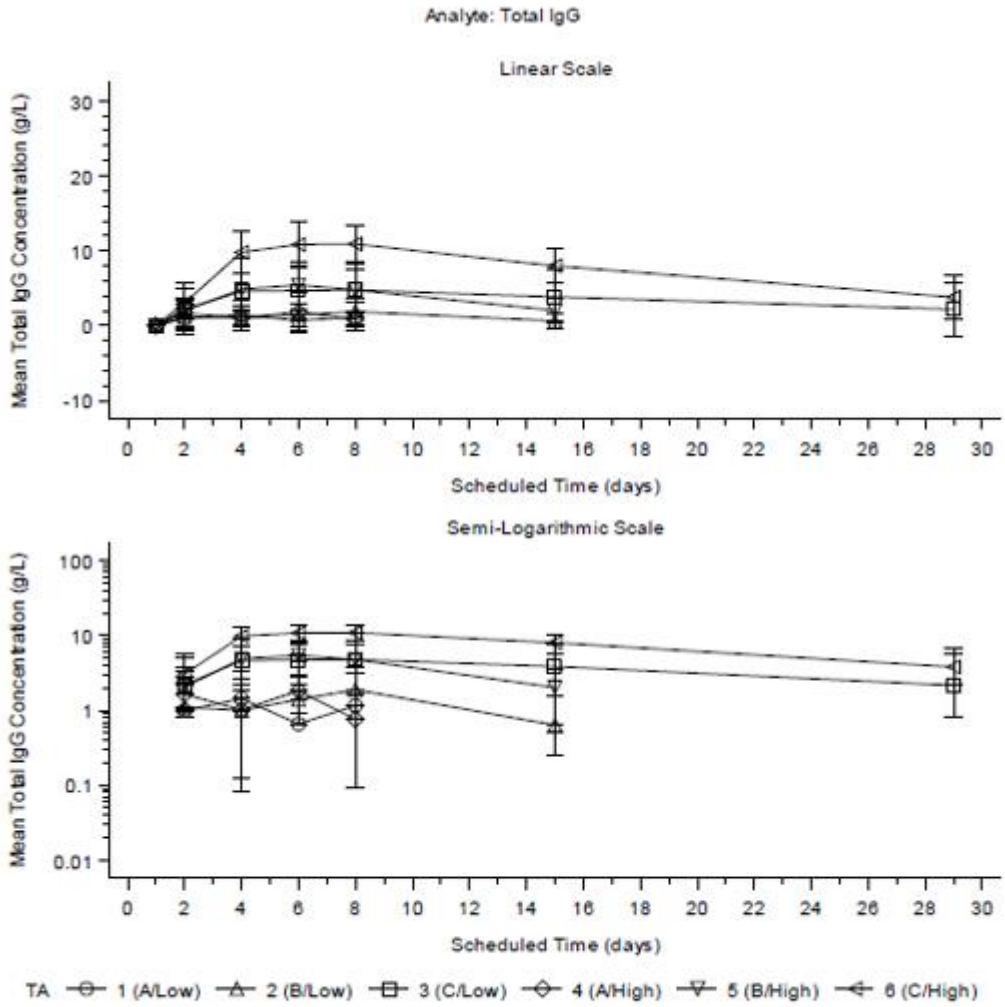
The AUC from time zero until the last quantifiable concentration (AUClast) can only be compared within the same treatment schedule due to the different sampling duration. Geometric mean AUClast for low and high TDLs of Sch-A was of 104.28 day*g/L and 111.07 day*g/L, respectively, with low variability (14.4% and 12.9%, respectively). Geometric mean AUClast for low and high TDLs of Sch-B were 222.36 day*g/L with low variability (10.4%) and 263.75 day*g/L with high variability (31.6%), respectively. Sch-C geometric mean AUClast was higher at the low TDL with a value of 378.57 day*g/L as opposed to high TDL of 324.75 day*g/L (Table 4). A very high variability could be observed for Sch-C with geometric mean %CV of 53.2% and 53.3% for the low and high TDL, respectively (**Table 5**).

Upon CHMP request the MAH provided baseline-uncorrected IgG PK data from Study TAK-771-1001 by BMI strata for 18 to <25 kg/m2 and ≥25 to 30 kg/m2. Overall, the exposure (AUC and Cmax) of total IgG was comparable between subjects with BMI 18 to <25 kg/m2 and subjects with BMI ≥25 to 30 kg/m2 with no consistent trends in directionality of the differences among ramp-up or dose level. Across all doses and ramp-up schedules, the median tmax tended to be slightly delayed in subjects with BMI ≥25 to 30 kg/m2, though the ranges of tmax values were similar.

Baseline-corrected Total IgG Concentrations and PK Parameters

Mean (±SD) serum baseline-corrected concentrations of total IgG vs scheduled time following SC administration of IGI, 10% with rHuPH20 to healthy adult subjects are presented by treatment arm in **Figure 2**.

Figure 2 Mean (±SD) Baseline-corrected IgG Serum Concentrations (g/L) vs Time by Treatment Arm on a Linear and Semi-Logarithmic Scale



IgG=immunoglobulin G; SD=standard deviation
Legend indicates treatment schedule in the following way Treatment Arm ([TA] Schedule/Target Dose Level).

Following SC administration of IGI, 10% with rHuPH20 to healthy subjects, mean baseline-corrected total IgG concentrations increased with time reaching a peak between 4 to 8 days post dosing and subsequently decreased, not reaching baseline values at the end of the sampling period (Day 8 for Sch-A, Day 15 for Sch-B, and Day 29 for Sch-C). The highest corrected total IgG level is observed for Treatment Arm 6 (sampling Sch-C, high TDL) followed by Treatment Arm 3 (sampling Sch-C, low TDL) and Treatment Arm 5 (sampling Sch-B, high TDL).

Baseline-corrected serum total IgG PK parameters following SC administration of IGI, 10% with rHuPH20 to healthy adult subjects are summarized by treatment arm in **Table 6**. Following baseline correction, multiple time points led to negative values and therefore the estimation of certain parameters was limited by the number of subjects with adequate data. Several subjects had 2 or fewer consecutive time points with measurable concentrations following baseline correction, therefore for some treatment arms only limited n was available for the calculation of the summary statistics for the PK parameters.

The terminal phase of total IgG could not be adequately estimated for most subjects with the exception of 2 subjects. Considering that limited number of data points following Cmax were available to generate a reliable log-linear regression, the following PK parameters could not be estimated, including AUC0-inf, λz, t1/2, CL/F, and VZ/F for most subjects.

Table 6 Summary of Baseline-corrected Total IgG Serum Pharmacokinetic Parameters by Treatment Arm (Pharmacokinetic Set)

PK parameter (unit) Dose on Day 1	TA 1, Schedule A, Low TDL (N=8) ¼ of TDL (0.1 g/kg)	TA 2, Schedule B Low TDL (N=8) ½ of TDL (0.2 g/kg)	TA 3, Schedule C Low TDL (N=8) Full TDL (0.4 g/kg)	TA 4, Schedule A High TDL (N=8) ¼ of TDL (0.25 g/kg)	TA 5, Schedule B High TDL (N=9) ½ of TDL (0.5 g/kg)	TA 6, Schedule C High TDL (N=10) Full TDL (1.0 g/kg)
C_{max} (g/L)						
n	2	3	7	5	9	10
Geometric mean	2.70	3.10	5.34	3.17	5.71	12.75
GM 95% CI	0.00, 11260.09	1.27, 7.55	3.40, 8.39	1.49, 6.74	4.22, 7.73	11.37, 14.31
GM %CV	116.8	37.1	51.9	66.8	41.0	16.2
t_{max} (day)						
n	2	3	7	5	9	10
Median	5.0	8.0	4.0	4.0	6.0	6.0
Min, max	2.0, 8.0	6.0, 16.0	4.0, 15.0	2.0, 8.0	4.0, 16.1	4.0, 8.0
$AUC_{0\text{-}D8}$ (day*g/L)						
n	2	3	7	4	9	10
Geometric mean	9.63	14.67	25.02	8.96	25.27	55.47
GM 95% CI	0.00, 40802025.66	5.72, 37.67	14.67, 42.69	4.67, 17.20	16.92, 37.76	47.93, 64.19
GM %CV	411.1	39.4	62.9	42.7	56.0	20.6
AUC_{last} (day*g/L)						
n	2	3	7	5	9	10
Geometric mean	9.63	31.60	70.39	9.49	42.48	117.69
GM 95% CI	0.00, 40802025.66	21.23, 47.03	34.97, 141.67	5.94, 15.14	30.88, 58.44	76.76, 180.44
GM %CV	411.1	16.1	87.9	39.0	43.3	65.5

AUC0-D8=area under the concentration-time curve from time zero (Day 1) to Day 8; AUClast=area under the curve from the time of dosing to the last measurable concentration; Cmax=maximum concentration; GM CV%=coefficient of variation of geometric mean; GM 95% CI=geometric mean 95% confidence interval; IgG=immunoglobulin G; max=maximum; min=minimum; N=number of subjects in the group; n=number of subjects with reported value; PK=pharmacokinetic; t_{max}=time of maximum observed concentration; TA=treatment arm; TDL=target dose level
Low TDL: 0.4 g/kg (Study Part 1); High TDL: 1.0 g/kg (Study Part 2).
TA 1 (Low TDL) & 4 (High TDL): Schedule A, 1/4 TDL (Days 1, 8), 1/2 TDL (Day 15), 3/4 TDL (Day 29), 1/1 TDL (Day 50).
TA 2 (Low TDL) & 5 (High TDL): Schedule B, 1/2 TDL (Day 1, Day 15), 1/1 TDL (Day 29, Day 57).
TA 3 (Low TDL) & 6 (High TDL): Schedule C, 1/1 TDL Day 1, Day 29, and Day 57.

The highest baseline-corrected peak concentration was observed for the high TDL of Sch-C with a geometric mean Cmax of 12.75 g/L. Geometric mean Cmax values observed for Treatment Arm 3 (Sch-C, low TDL) and Treatment Arm 5 (Sch-B, high TDL) were similar, with values of 5.34 g/L and 5.71 g/L, respectively. Geometric mean Cmax for the remaining treatment arms ranged from 2.70 g/L to 3.17 g/L. An increase by 2.5-fold in dose administered on Day 1 (from low TDL to high TDL) led to an increase in geometric mean Cmax by 1.17-, 1.84-, and 2.39-fold for Schedules A, B, and C, respectively. Geometric mean Cmax increased by about the same fold (2.23-fold) as the administered dose on Day 1 between Sch-B high TDL (0.5 g/kg) and Sch-C high TDL (1.0 g/kg) (2-fold). Similarly, geometric mean Cmax increased almost by the same fold (1.72-fold) as the dose increase between Sch-B low TDL (0.2 g/kg) and Sch-C low TDL (0.4 g/kg) (2-fold). A similar fold increase (4.02-fold) was also observed between baseline-corrected geometric mean Cmax at high TDL of Sch-C (dose on Day 1: 1.0 g/kg) as compared to high TDL of Sch-A (dose on Day 1: 0.25 g/kg) (4-fold). Inter-subject variability was generally high, however, for Treatment Arm 1 (Sch-A, low TDL) only data from 2 subjects was available and variability could not be estimated adequately (**Table 6**). Median time to reach Cmax ranged from 4.0 to 8.0 days post dose, with individual values ranging from 2.0 to 16.1 days post dose (**Table 6**).

The exposure up to Day 8 (AUC0-D8) of sampling was the lowest for Sch-A, with geometric mean baseline-corrected AUC0-D8 of 9.63 day*g/L and 8.96 day*g/L for the low and high TDL, respectively. Similar exposure was observed within Treatment Arm 3 (Sch-C, low TDL) and Treatment Arm 5 (Sch-B, high TDL) with geometric mean AUC0-D8 of 25.02 day*g/L and 25.27 day*g/L, respectively. The highest exposure up to Day 8 was observed for Treatment Arm 6 Sch-C, high TDL with a geometric mean AUC0-D8 of 55.47 day*g/L. An increase in geometric mean AUC0-D8 by 1.72- and 2.22-fold was observed for the 2.5-fold increase in administered dose on Day 1 within Schedule B and C, respectively. Geometric mean AUC0-D8 increased by about the same fold (2.20-fold) as the administered dose on Day 1 between Sch-B high TDL (0.5 g/kg) and Sch-C high TDL (1.0 g/kg) (2-fold). Similarly, geometric mean AUC0-D8 increased almost by the same fold (1.71-fold) as the dose increase between Schedule-B low TDL (0.2 g/kg) and Sch-C low TDL (0.4 g/kg) (2-fold). Inter-subject variability was generally moderate to very high with geometric %CV ranging from 20.6% to 62.9%, excluding Treatment Arm 1 (low TDL, Sch-A) that had only 2 observations included so that variability could not be reliably estimated (**Table 6**).

The baseline-corrected exposure from time zero until the last quantifiable concentration (AUClast) is compared only between low and high TDL within Sch-A, Sch-B and Sch-C. The highest geometric mean AUClast was observed for Sch-C low and high TDL of 70.39 day*g/L and 117.69 day*g/L, respectively (**Table 6**). Inter-subject variability was generally very high for Sch-C with geometric mean %CV of 87.9% and 65.5% for low and high TDL, respectively.

Study 161403

Study Description

Study 161403 was a pivotal Phase 3 study in adult subjects with CIDP to evaluate the efficacy, safety and tolerability of HyQvia. Serum trough total IgG levels were also assessed throughout the study. The study consisted of 2 study parts. In Study Epoch 1, subjects received either HyQvia or a 0.25% albumin placebo solution with rHuPH20 SC in a double-blind fashion for a period of 6 months, or until relapse. The dosing regimen for investigational product (IP) was the same as the subject's pre-randomization monthly equivalent IgG dose (or at matching infusion volume for subjects in the placebo group) when administered at a dosing frequency of every 2, 3, or 4 weeks.

Subjects who met relapse criteria during Epoch 1 and entered Epoch 2, were offered open-label IVIg. The induction dose was 2 g/kg body weight administered intravenously in divided doses over 2 to 5 consecutive days, followed by maintenance infusions at the same monthly dose as the subject's pre-randomization IVIg doses administered every 3 weeks for 6 months. A total of 138 subjects were randomized and 132 (95.7%) were dosed with IP. Of the 132 dosed subjects, 94 subjects (n=48 for HyQvia, n=46 for placebo) completed Epoch 1. A total of 28 subjects developed a relapse in Epoch 1, and 21 of those enrolled in Epoch 2. All 21 subjects completed Epoch 2.

Only Epoch 1 data are presented in the following sections since Epoch 2 does not involve HyQvia.

Total IgG Pharmacokinetics Summary (Epoch 1)

Blood samples were collected at multiple time points from all subjects in both study epochs to determine serum trough levels of total IgG. At screening/baseline, serum IgG samples were collected prior to the start of the pre-randomization IVIg infusion. During Epoch 1, serum trough IgG samples were collected on the Epoch 1 Week 1 (E1W1), Epoch 1 Week 3, Epoch 1 Week 5, Epoch 1 Week 9, Epoch 1 Week 15/Epoch 1 interim (E1INT), and Epoch 1 Week 27/End of Epoch 1 (EOE1T) visits (or on the first day of IP infusion if the IP dose was administered as divided doses over multiple days) prior to the start of the infusion.

Summary of Serum Total IgG Trough Data

Serum trough levels of total IgG in Epoch 1 are provided in **Table 7**. Mean observed baseline values (ie, prior to the first administration of Epoch 1 treatment and after the last IVIg administration) were comparable between the HyQvia and placebo treatment groups. Mean observed values of ([E1W1], immediately prior to administration of Epoch 1 treatment on Study Day 1) were comparable to the baseline values and between treatment groups. The E1INT observed values were lower than values reported at E1W1 for both treatment groups, and the mean value was higher in the HyQvia group than the placebo group. The general decrease of serum IgG trough levels in the HyQvia group was likely driven by the lower administered doses during the ramp-up period where subjects received partial doses. The EOE1T/early termination (ET) values were comparable to those at E1INT, indicating that serum trough levels of total IgG remain stable after dose was stabilized, and as expected, the mean value was higher in the HyQvia group than the placebo group. The HyQvia observed values were higher at all visits compared to those reported for placebo. Inter-subject variability as indicated by SD is rather high for both cohorts.

Although mean serum total trough IgG levels were lower after HyQvia (from 1847.9 to 1528.4 mg/dL, ratio of geometrics means: 0.83, 95% CI: 0.76-0.90), the baseline samples were not systematically collected immediately prior to the last IVIg dose (as per protocol), and even in some instances, the samples were obtained prior to week 1 IMP infusion (approximately 2 weeks after the last IVIg infusion). Hence, the reduction in trough levels should be interpreted with caution.

In Study 161403, the ratio of geometric means (end of Epoch 1 treatment [EOE1T]/early termination [ET] relative to baseline) indicated a similar reduction in trough IgG levels with or without relapsed and/or early discontinued subjects excluded. The reported bioavailability of HyQvia relative to IVIg, estimated in the primary immunodeficiency disease (PID) population (Li et al. 2023) should also be considered when comparing the trough levels between HyQvia and IVIg.

Table 7 Summary of Serum Total Trough IgG Levels in Epoch 1 by Treatment Group and Visit (Epoch 1 MITT Analysis Set)

	Placebo (N = 70)		HYQVIA (N = 62)		Total (N = 132)	
Timepoint Statistic	Observed Value	CFB	Observed Value	CFB	Observed Value	CFB
Serum IgG (mg/dL)						
Baseline [a]		NA		NA		
n	65		57		122	
Mean (SD)	1824.2 (478.09)		1847.9 (511.84)		1835.3 (492.22)	
Geometric Mean (SD)	1764.8 (1.30)		1780.4 (1.32)		1772.1 (1.31)	
Median	1690.0		1780.0		1745.0	
Q1, Q3	1500.0, 2110.0		1450.0, 2170.0		1500.0, 2150.0	
Min, Max	926, 3310		1020, 3120		926, 3310	
E1W1						
n	63		55		118	
Mean (SD)	1831.7 (483.80)		1872.9 (502.78)		1850.9 (491.05)	
Geometric Mean (SD)	1770.7 (1.30)		1808.8 (1.31)		1788.4 (1.30)	
Median	1750.0		1810.0		1790.0	
Q1, Q3	1500.0, 2140.0		1500.0, 2180.0		1500.0, 2150.0	
Min, Max	926, 3310		1060, 3120		926, 3310	

Timepoint Statistic	Placebo (N = 70)		HYQVIA (N = 62)		Total (N = 132)	
	Observed Value	CFB	Observed Value	CFB	Observed Value	CFB
E1INT						
n	44	40	47	44	91	84
Mean (SD)	1129.2 (270.61)	-590.0 (370.81)	1473.9 (347.52)	-383.3 (379.20)	1307.2 (355.98)	-481.8 (387.16)
Geometric Mean (SD)	1095.3 (1.29)		1434.7 (1.27)		1259.2 (1.32)	
Median	1085.0	-543.5	1470.0	-262.5	1270.0	-454.5
Q1, Q3	959.5, 1320.0	-784.5, -370.0	1220.0, 1650.0	-635.0, -100.0	1040.0, 1560.0	-700.0, -130.0
Min, Max	449, 1690	-1513, 40	755, 2510	-1520, 200	449, 2510	-1520, 200
EOE1T/ET						
n	45	41	47	43	92	84
Mean (SD)	1244.4 (593.90)	-451.1 (625.85)	1528.4 (430.31)	-356.2 (501.63)	1389.5 (533.40)	-402.5 (564.25)
Geometric Mean (SD)	1169.4 (1.38)		1475.0 (1.30)		1316.7 (1.37)	
Median	1160.0	-510.0	1490.0	-250.0	1315.0	-439.5
Q1, Q3	957.0, 1340.0	-780.0, -170.0	1270.0, 1660.0	-650.0, -30.0	1100.0, 1560.0	-720.0, -125.0
Min, Max	696, 4680	-1682, 2370	855, 2880	-1820, 690	696, 4680	-1820, 2370

CFB=Change from baseline; IP=Investigational product; MITT=Modified Intent-to-Treat; BL=Baseline; ET=Early termination; IgG=Immunoglobulin G; mg=Milligram; dL=Deciliter; Q1=1st quartile; Q3=3rd quartile; SD=Standard deviation; n=Number of subjects who had a baseline value and a post-baseline value
Analysis visits: E1Wn: Epoch 1 Week n, E1INT: Epoch 1 Interim, EOE1T: End of Epoch 1 Treatment.
Epoch 1 Modified Intent-to-Treat Analysis Set includes all randomized subjects who received any double-blind IP.
Results from planned visits are presented in this table.
[a] Epoch 1 baseline value is defined as the pre-SC treatment baseline visit value, if nonmissing. If missing, then the Screening visit value is used (if nonmissing).

Serum trough levels vs relapse status

Serum trough levels of total IgG in Epoch 1 after Day 120 or at the time of CIDP relapse are summarized in **Table 8**. Mean serum total trough IgG levels were higher in subjects in the HyQvia group at both the time of relapse for subjects who developed a relapse (n=6), and after Day 120 for subjects who did not develop a relapse (n=39), for subjects with both baseline and post-baseline serum total trough IgG values. However, there did not appear to be any meaningful difference in serum IgG levels between relapsed and non-relapsed subjects in either the placebo or HyQvia groups. Given the small number of relapsed subjects and high inter-subject variability, this data should be interpreted with caution.

The serum total trough IgG levels over time in Epoch 1 by treatment arm and relapse status revealed no apparent correlation between the total serum IgG level and the occurrence of relapse in both treatment arms (**Table 8**). In some subjects, relapse occurred when serum IgG trough levels were higher than baseline values, whereas in others, there was a decline. The exact reason for this observed discordance between change in serum total IgG level and the occurrence of relapses is not fully known, but could be due to inter-individual differences in treatment response.

Table 8 Summary and Analysis of Change from Pre-Subcutaneous Treatment Baseline in Serum Total Trough IgG Levels in Epoch 1 by Relapse Status (Epoch 1 MITT Analysis Set)

Timepoint Statistic	Subjects Who Relapsed [d]		Subjects Who Did Not Relapse [d]	
	Observed Value	Change from Baseline	Observed Value	Change from Baseline
Serum Total Trough IgG Level (mg/dL)				
HyQvia Arm				
Baseline [a]				
n	6		45	

	Subjects Who Relapsed [d]		Subjects Who Did Not Relapse [d]	
Timepoint Statistic	**Observed Value**	**Change from Baseline**	**Observed Value**	**Change from Baseline**
Mean (SD)	1716.7 (417.64)		1863.6 (542.38)	
Median	1670.0		1810.0	
Q1, Q3	1350.0, 1880.0		1450.0, 2180.0	
Min, Max	1300, 2430		1020, 3120	
Time of Relapse/After Day 120 [b]				
n	6	6	39	39
Mean (SD)	1612.5 (548.98)	-104.2 (613.53)	1511.3 (407.09)	-386.2 (502.19)
Median	1680.0	-85.0	1480.0	-250.0
Q1, Q3	1110.0, 1950.0	-480.0, 210.0	1270.0, 1620.0	-700.0, -30.0
Min, Max	895, 2360	-985, 800	927, 2880	-1820, 690
Median ratio (Relapse/No Relapse) of change from Baseline [c]				1.178
95% CI of the Median ratio [c]				0.837, 1.532
Placebo Arm				
Baseline [a]				
n	21		42	
Mean (SD)	2032.2 (589.27)		1706.2 (382.98)	
Median	1990.0		1600.0	
Q1, Q3	1630.0, 2350.0		1480.0, 2000.0	
Min, Max	926, 3310		1080, 2560	
Time of Relapse/After Day 120 [b]				
n	18	18	36	36
Mean (SD)	1455.4 (872.86)	-660.1 (873.87)	1144.3 (256.75)	-501.5 (443.05)
Median	1185.0	-662.5	1125.0	-505.0
Q1, Q3	1080.0, 1460.0	-1000.0, -520.0	941.0, 1335.0	-777.5, -175.5
Min, Max	783, 4680	-1850, 2370	696, 1610	-1682, 470
Median ratio (Relapse/No Relapse) of change from Baseline [c]				0.899
95% CI of the Median ratio [c]				0.758, 1.062

BL=baseline; CI=Confidence interval; dL=Deciliter; E2W1=Epoch 2, Week 1; EOE1/ET=End of Epoch 1/early termination; IgG=Immunoglobulin G; INCAT=Inflammatory Neuropathy Cause and Treatment; IP=Investigational product; IV= Intravenous; Max=Maximum; mg= Milligram; Min=Minimum; MITT=Modified Intent-to-Treat; n=number; Q1=1st quartile; Q3=3rd quartile; SC=Subcutaneous; SD=Standard deviation;

Epoch 1 MITT analysis set includes all randomized subjects who received any double-blind IP.

[a] Baseline is defined as the last non-missing value before the first administration of IP.

[b] For subjects who relapsed, the sample collected at the Pre-IV BL/E2W1 visit was used. If missing, then the first sample after the relapse date was used. For subjects who did not relapse, the last recorded IgG level on double-blind treatment [E0E1T/ET visit] was used. Subjects who did not relapse and who had no IgG results after Day 120 are not included. Subjects with missing relapse status are not included.

[c] Median ratio in changes from baseline based on the Hodges-Lehmann (HL) estimator. The HL estimator and the corresponding two-sided 95% CI on changes from baseline (based on log-transformed Serum total trough IgG) between subjects who relapsed and subjects who did not relapse. Results are back-transformed and provide the median ratio in changes from baseline and the corresponding two-sided 95% CI.

[d] Relapse is defined as an increase of ≥ 1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores obtained not more than 7 days apart. The number (N) for each relapse group and treatment are the number with non-missing relapse status and non-missing Serum Total Trough IgG results.

Trough Serum IgG Subgroup Analyses (Epoch 1)

In the pivotal Phase 3 study 161403, additional subgroup analyses of relapse rate, the primary endpoint of Epoch 1, were done to determine any statistically significant differences observed in subgroups of interest. These subgroups included the following: age (≤55 years, >55 years), sex (male, female), race (White, American Indian or Alaska Native, Multiple Races), dosing regimen (every 2, 3, and 4 weeks), geographic region (North America, South America, and Europe), relapse status, BMI group, diabetes status, and two clinical measures of functional worsening were also investigated.

Multiple pairwise comparisons were performed using Wilcoxon tests for the visits in Epoch 1 (E1W1, E1Int, and EOE1T) as the data allowed. For the two clinical measures of functional worsening, comparisons were only carried out for the EOE1T visit. A p-value of <0.05 was considered to be statistically significant. This subgroup analysis sought to evaluate trends in trough serum IgG levels based on treatment (HyQvia vs placebo) and by subgroups of interest. Overall, the analysis showed that there was a significant treatment effect on trough serum IgG levels between HyQvia and placebo, ie, trough serum IgG levels were higher for HyQvia treated subjects compared to subjects treated with placebo and that few trends emerged for the various subgroups evaluated.

Within each treatment group (HyQvia or placebo), trough serum IgG levels were comparable by age group (≤55 years, >55 years), sex (male, female), and BMI group (Underweight, Normal Weight, Overweight, Obese). With a large majority of the subjects being White, the effect of race could not be fully evaluated. Additionally, dosing regimen (every 3 weeks vs every 4 weeks) had no apparent effect on trough serum IgG levels though the number of subjects with regimens other than every 4 weeks were limited. For geographic region among subjects treated with HyQvia, there was a trend towards lower trough serum IgG levels in subjects from Europe, compared to those from subjects in North America or South America, though number from these other regions were too limited to draw conclusions.

As there were statistically significant differences in the trough serum IgG levels at baseline prior to treatment when categorized by diabetes status and treatment, analyses of this subgroup are confounded, and the results of this subgroup analyses should be interpreted with caution. In subjects with diabetes, median trough serum IgG levels were comparable between subjects treated with placebo and those treated with HyQvia and were comparable to those of non-diabetic subjects treated with placebo, whereas trough serum IgG levels tended to be higher in non-diabetic subjects treated with HyQvia.

Analyses of the two functional worsening subgroup categories demonstrate that higher trough serum IgG levels were observed in subjects treated with HyQvia than with placebo where functional worsening was not observed by hand grip strength or Inflammatory Neuropathy Cause and Treatment disability score. In contrast, the IgG levels were comparable between subjects treated with HyQvia and those treated with placebo where functional worsening was observed. Together these results suggest a possible correlation between trough serum IgG levels and the clinical responses in CIDP.

Comparison of serum total IgG through Level in HyQvia CIDP and PID.

The ratios of trough levels of IgG in CIDP vs in PID as well as the percentage difference of trough levels (using PID as reference) were calculated based on data from the ADVANCE-1 study (CIDP) and Studies 160602 and 160603 (PID). The results are presented in **Table 9** below.

Table 9 Comparison of Serum Total IgG Through levels (g/L) in HyQvia CIDP (161403) and PID (160602 & 160603) Studies

Study	Patient Population	N	Median Trough Level	Trough Ratio (% Difference), PID as Reference
161403	CIDP	47	14.9	NA
160602	PID	10	10.9	1.37 (36.6)
160603	PID	81	10.5	1.42 (41.9)

CIDP=chronic inflammatory demyelinating polyradiculoneuropathy; EOE1T=end of epoch 1 therapy; IgG=immunoglobulin G; NA=not applicable; PID=primary immunodeficiency diseases.
N=number of all HYQVIA treated subjects with available serum IgG data.
IgG data from visit 'End of Study' for Study 160602, visit 'End of Epoch 2' for Study 160603, and visit 'EOE1T' for Study 161403 is considered for the analysis.

2.3.3. Discussion on clinical pharmacology

In the study TAK-771-1001, the PK of total serum IgG and IgG subclasses was evaluated as a secondary endpoint in healthy adult volunteers following a single SC administration of HyQvia at doses ranging from 0.1 to 1 g/kg (doses on day 1). Subjects received IGI 10% either from a partial TDL dose to a full TDL dose with a Ramp-Up dosing schedule or directly at the full TDL dose without a Ramp-Up. The TDLs were 0.4 g/kg and 1.0 g/kg for Study Part 1 and Study Part 2, respectively. Each part of the study consisted of three treatment arms with different Ramp-Up schedules. A total of 51 healthy adult subjects were enrolled, of which a total of 38 (74.5%) subjects completed the study and 13 (25.5%) subjects discontinued the study.

The PK results of this study indicate that baseline-corrected geometric mean Cmax and AUC0-D8 increased by approximately the same fold as the increasing dose administered on Day 1. A 2.5-fold increase in the dose administered on day 1 resulted in increases in geometric mean Cmax by 1.17-, 1.84-, and 2.39-fold for schedule A, B, and C, respectively. A 1.72- and 2.22-fold increase in geometric mean AUC0-D8 was observed for the 2.5-fold increase in administered dose on day 1 for schedule B and C, respectively.

However, inter-subject variability based on geometric mean %CV was generally high for baseline-corrected Cmax and AUC0-D8 parameters (ranging 16.2-66.8% in for treatment arms 2 to 6). Variability for baseline-corrected values was moderate to high, and low to moderate for baseline-uncorrected values. The MAH provided two publications that have also reported high inter-subject variability in trough IgG values in CIDP (Rajabally et al. 2013; van Doorn et al. 2011).

The terminal phase of total IgG could not be adequately estimated for most subjects with the exception of 2 subjects. Thus, only limited observations following Cmax were available to generate a reliable log-linear regression, and no reliable estimation of terminal phase parameters of IgG (AUC0-inf, CL/F, Vz/F, λz and t1/2) was possible. Nevertheless, the PK profile of HyQvia (and other IG preparations) is already well described and it is not expected that a ramp up dosing has a significant impact on this. Upon CHMP request, available PK data for both BMI strata within each treatment arm were submitted, no clear trends indicating that BMI has an influence on IgG trough levels were visible.

Study 161403 was a pivotal Phase 3 study conducted in two epochs. In Epoch 1, subjects were randomized to either HyQvia or placebo. At various time points, blood samples were collected during Epoch 1. The mean serum trough levels of total IgG for subjects receiving HyQvia treatment decreased during the treatment ramp-up period (until E1INT), then remained stable throughout the treatment period (>800mg/dl). A possible explanation for the delayed drop in trough IgG levels may be a carry-over effect from previous IVIG treatment which can last up to 12 weeks. These time intervals may overlap with the E1INT measurement when lower levels were first seen. Overall, observed values in the HyQvia arm were significantly higher compared to those reported for placebo. However, trough IgG levels are

typically higher with SCIg than IVIg (e.g. Berger et al., 2010). This may be due to typically higher doses with SCIgs. HyQvia treatments resulted in lower trough IgG levels than previous IVIg treatments (probably due to the lower bioavailability). The MAH was requested to discuss whether it should be recommended to use higher doses of HyQvia than previous IVIg. The MAH noted that the reduced bioavailability of HyQvia and the different dosing frequency compared to IVIg (approximately 79%-93.3%, Li et al., 20/23) should be considered when interpreting the reduction in trough levels with HyQvia compared to IVIg. Furthermore, the MAH provided several considerations as to why the observed reductions in trough IgG levels in patients with CIDP are not clinically significant and that no clear relationship between lower IgG trough levels and disease worsening can be concluded. This was agreed by the CHMP. Therefore, a general recommendation for the use of higher doses of HyQvia is not required. Instead, the applicant added a statement regarding dose reductions or modifications according to the individual clinical response in section 4.2 of the SmPC.

Serum trough total IgG levels at the time of relapse in subjects who relapsed compared to steady-state trough levels (after day 120) in subjects who did not relapse did not reveal any meaningful differences. However, there is uncertainty due to the relatively high inter-subject variability, a small sample size for subjects who relapsed on HyQvia (n=6) and a possible carry-over effect of pre-study IVIg. The influence of diabetes status on IgG levels has been discussed, but this should be interpreted with caution due to the differences seen at baseline between non-diabetic and diabetic subjects. In addition, no direct comparison of HyQvia and IVIg has been performed and in general, the optimal PK parameters for the treatment of CIDP are currently unknown.

Overall, only the serum trough levels of total IgG were assessed in the study, this information has been added in section 5.2 of the SmPC. In addition the median serum trough levels of total IgG in CIDP were compared to the median serum trough levels of total IgG in PID, they were 40% greater than in PID. This was also added in section 5.2 of the SmPC.

Dose Ramp Up schedule recommendations from IVIg to HyQvia:

Dose escalation recommendations for starting HyQvia infusions in patients previously treated with IVIg have been provided by the MAH. This dosing regimen was also used in the pivotal study. A dose Ramp-Up guidance comparable to Schedule Arm A of the study TAK-771-1001 has been incorporated into the section 4.2 of the SmPC and is considered acceptable. The initial dose of HyQvia is administered 2 weeks after the last IVIg dose. The initial dose is calculated by dividing the last IVIg dose by IVIg dosing interval in weeks (weekly-equivalent dose). One week after the initial dose, another weekly-equivalent dose is administered. Subsequent infusions are administered with gradually increasing doses and dose intervals considering volume, total infusion time, and tolerability of infusions. A typical ramp-up period takes 4 to 9 weeks, depending on the dosing interval and tolerability. Accelerated ramp-up can be considered depending on the need as per the physician's discretion and if SC injection volumes can be tolerated. Doses less than or equal to 0.4 g/kg may be administered without a ramp up per physician discretion and provided acceptable patient tolerance.

2.3.4. Conclusions on clinical pharmacology

The results of the Study TAK-771-001 indicate that the ramp-up dosing schedule is feasible and results in stable IgG trough levels. More importantly, the ramp-up schedule may help the patient to adapt to the large SC doses while becoming comfortable with HyQvia administration, resulting in fewer TEAEs and improved tolerability (as discussed in clinical safety section).

PK data obtained from the study 161403 suggest that treatment with HyQvia results in stable IgG levels over time. There was no strong correlation between trough total IgG levels and the occurrence of relapses; the relapse rate with HyQvia was comparable to published rates with IVIg or SCIg. However, slightly lower trough IgG levels with HyQvia were observed than with pre-study IVIg/ baseline. As no direct comparison of SCIg and IVIg treatments in CIDP patients has been performed, it remains open whether lower levels lead to disease deterioration. So far, the optimal PK parameters for the treatment of

CIDP are still unknown. Patients may benefit from continued IVIg maintenance treatment by maintaining stable IgG trough and peak levels. There may be considerable individual variability in the dose and treatment intervals required to achieve and maintain a clinical response. Such a statement has been added in section 4.2 of the SmPC.

Overall, the clinical pharmacology package supports the extension of indication to CIDP patients, and the proposed dosing frequency is acceptable from the PK point of view.

2.4. Clinical efficacy

2.4.1. Main study

Study 161403: A Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HyQvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID/KIOVIG) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Study 161403 was a Phase 3, prospective, multicentre, double-blind, randomised, placebo-controlled study to evaluate the efficacy, safety, and tolerability of HyQvia and IGI (Human), 10% (GGL/KIOVIG) for the treatment of CIDP. The study enrolled adult subjects with a confirmed diagnosis of CIDP who had remained on a 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 IVIg therapy for at least 12 weeks prior to screening.

Methods

The overall study design is shown in

Figure 3 Study Design Schematic. The study consisted of the following:

- A screening/baseline period of up to 8 weeks.
- An SC treatment period (Epoch 1) of up to 6 months.
- An IV treatment period (Epoch 2) of 6 months, for subjects who relapsed during Epoch 1.

The maximum overall duration of this study was estimated to be approximately 72 months from study initiation (ie, first subject enrolled) to study completion (ie, last subject last visit). The planned duration of subject participation was approximately 8 to 14 months, from enrolment to study completion. For subjects who completed Epoch 1 without relapse, the duration of study participation was approximately 8 months. Subjects who reached the end of Epoch 1 were able to consent to roll over into an open-label long term extension study (Study 161505). For subjects who relapsed during Epoch 1 and subsequently entered Epoch 2, the duration of study participation was lower than 14 months in the study as the relapsed subjects did not complete 6 months in Epoch 1. The maximum duration of study participation was 14 months.

Epoch 1: Subcutaneous Treatment Period

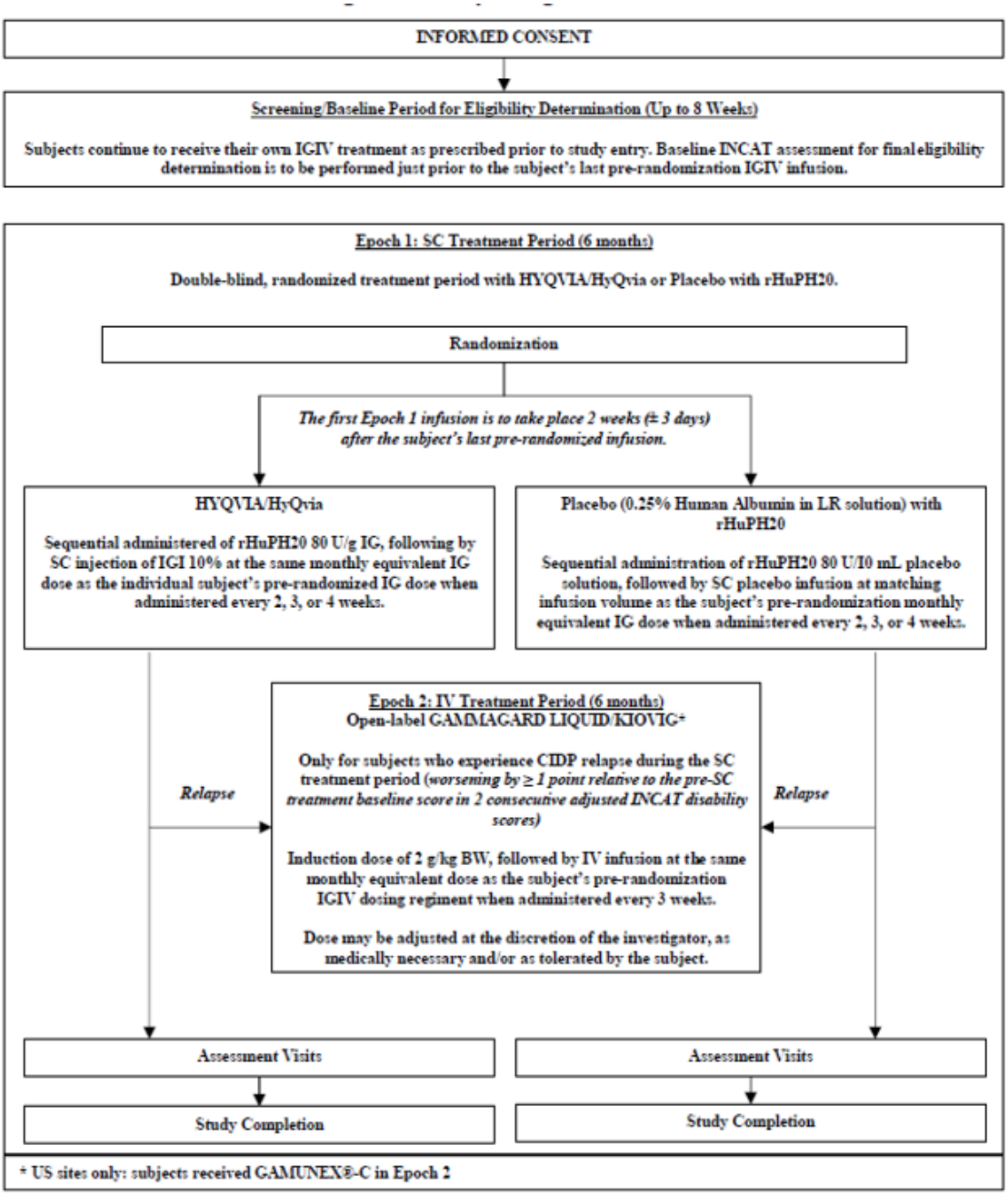
Epoch 1 of the study was double-blind and placebo-controlled. Eligible subjects were randomized in a 1:1 ratio to receive either HyQvia or the 0.25% albumin placebo solution with rHuPH20 in a double-blind fashion for a period of 6 months or until relapse.

Assessments were conducted to monitor for changes in the subject's functional ability (Inflammatory Neuropathy Cause and Treatment [INCAT] disability score), activities of daily living (ADL) (Rasch-built Overall Disability Scale: R-ODS), hand grip strength, and muscle strength (Medical Research Council [MRC] sum score). Additional assessments included serum trough IgG levels, as well as safety laboratory assessments. Patient reported outcome (PRO) measures were collected, including quality of life (Short form-36 health survey [SF-36]), health utility status (EuroQoL [European Quality of Life]-5 Dimensions [EQ-5D] scores), treatment satisfaction, treatment preference, and PGIC. An electronic diary (DIARYpro) was utilized to capture data related to infusions, subject notes related to adverse events (AEs) and concomitant medications, and PRO measures such as R-ODS and HRU. At any time during the SC treatment period, unscheduled visits for INCAT assessments were allowed for subjects who experienced CIDP worsening, in order to determine whether the worsening met the definition of relapse (ie, worsening in functional disability by ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores obtained less than 7 days apart.

Open-label treatment with IVIg was provided to any subject (regardless of their treatment assignment in Epoch 1) who met the definition of relapse and agreed to Epoch 2, in order to restore functional ability. An INCAT assessment was performed at the time the subject was evaluated for relapse, and again prior to the initiation of IVIg treatment in Epoch 2. The pre-IV treatment baseline INCAT assessment was used to confirm the subject's adjusted INCAT disability score had increased by ≥1 point relative to the pre-SC treatment baseline score, at which time the final determination of whether a subject had met relapse criteria was made. Subjects who relapsed during Epoch 1 could choose not to enter Epoch 2. For those subjects, INCAT assessments were repeated during the early termination visit and this INCAT disability score served to confirm whether the subject had met the relapse criteria.

The focus of this module is on 161403 Epoch 1 and does not include Epoch 2 as it was not evaluating HyQvia.

Figure 3 Study Design Schematic



Study participants

Subjects had to be ≥18 years of age (male or female) at the time of screening; had a documented diagnosis of definite or probable CIDP as confirmed by a neurologist specializing in neuromuscular diseases to be consistent with the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) 2010 criteria; had responded to IgG treatment in the past (partial or complete resolution of neurological symptoms and deficits) and was on a stable dose of intravenous immunoglobulin (IVIg) treatment within the dose range equivalent to a cumulative monthly dose of 0.4 to 2.4 g/kg body weight (BW, inclusive) administered intravenously for at least 12 weeks prior to screening; and had an inflammatory neuropathy cause and treatment (INCAT) disability score between 0 and 7 (inclusive). Subjects with focal atypical CIDP, pure sensory atypical CIDP, multifocal motor neuropathy or secondary neuropathies, or had received immunomodulatory/immunosuppressive agents within 6 months prior to screening, or had received corticosteroids 8 weeks prior to screening were excluded from the study.

Treatments

The dosing regimen for HyQvia or 0.25% albumin placebo with rHuPH20 was the same as the subject's pre-randomisation monthly equivalent immunoglobulin G (IgG) dose (or at matching infusion volume for subjects in the placebo group) when administered at a dosing frequency of every 2, 3, or 4 weeks. No conversion factor was applied when switching from pre-randomisation IVIg to HyQvia (or 0.25% albumin placebo with rHuPH20) treatment, ie, the monthly IgG dose of HyQvia (or matching infusion volume for subjects in the placebo group) were the same as the subject's pre-randomisation monthly dose of IVIg. The number of infusion visits and clinic visits during the SC treatment period varied across subjects depending on whether their infusion cycles were every 2, 3, or 4 weeks.

The study product components of HyQvia (or 0.25% albumin placebo with rHuPH20) were administered sequentially. The SC infusion of rHuPH20 solution at a dose of 80 U/g IgG (or its equivalent at 80 U/10 mL of the 0.25% albumin placebo solution) was administered first, followed by SC infusion of HyQvia (IGI 10%) or 0.25% albumin placebo solution within 10 minutes of completion of the infusion of rHuPH20 solution. To gradually increase the SC infusion volume, a dose ramp-up schedule was employed until the subject's full dose was reached. The first SC administration took place 2 weeks (±3 days) following the subject's last pre-randomisation IVIg administration.

The initial SC infusions (ie, infusions during the ramp-up period and, at a minimum, the first full-dose infusion) were administered at the study site or infusion centre to monitor for safety and tolerability, to determine the infusion rate and infusion volume per infusion site that can be tolerated by the subject, and to provide training to the subject (and/or, as applicable, to a caregiver who may assist the subject with self-infusion) on self-infusion procedures. At the investigator's discretion, the remainder of the SC infusions could have taken place at the study site, infusion centre, or at the subject's home or other suitable location, as acceptable per local regulations and standard practices of the study site. The ability of the subject (and/or caregiver) to perform infusion procedures independently was a pre-requisite for self-administration.

Training and the investigator/designee's evaluation of the subject's (and/or caregiver's) proficiency in independently self-administering infusions were documented.

Table 10 Dosing Ramp- up Schedule

Dosing Schedule	Study Visit												
	Pre-SC BL	W1 (2 Wks After Pre-SC BL)	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12
Q2W	Last full IGIV dose	1-W	1-W	2-W (full dose) and every 2 weeks thereafter									
Q3W		1-W	1-W	2-W	-	3-W (full dose) and every 3 weeks thereafter							
Q4W		1-W	1-W	2-W	-	3-W	-	-	4-W (full dose) and every 4 weeks thereafter				

Objectives

The purpose of the study was to provide evidence for the use of HyQvia as a maintenance therapy option that enables self-infusion of a full therapeutic dose every 2 to 4 weeks in subjects with CIDP. Additionally, the study aimed to provide evidence for the use of GGL/KIOVIG as an IVIg treatment option in patients with CIDP.

Primary Objective

1. To evaluate the efficacy of HyQvia as a maintenance therapy for CIDP to prevent relapse of neuromuscular disability and impairment.

Secondary Objectives

1. To assess the time to CIDP relapse during maintenance therapy with HyQvia, compared to placebo.
2. To assess the effect of HyQvia on activities of daily living (ADL).
3. To assess the safety and tolerability of HyQvia.
4. To monitor for the presence of binding and neutralizing anti-rHuPH20 antibodies following HyQvia administration.

Tertiary Objectives

1. To evaluate the effects of HyQvia on additional clinical outcome measures, including change in functional ability, hand grip strength, and muscle strength.
2. To evaluate improvement in functional impact on everyday tasks as measured by a prespecified subscore of Rasch-built Overall Disability Scale (R-ODS).
3. To assess the effect of HyQvia on quality of life, health utility, health resource utilization (HRU), treatment satisfaction, treatment preference, and patient global impression of change (PGIC).
4. To assess the effect of HyQvia on the total number or appearance of new demyelinating abnormalities (DAs) on electrodiagnostic (EDX) studies.

Outcomes/endpoints

Primary endpoint

1. Relapse rate (proportion of subjects who experienced a worsening of functional disability defined as an increase of ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores obtained less than 7 days apart).

Secondary endpoints

Efficacy

1. Proportion of subjects who experienced a worsening of functional disability defined as one or more of the following: an increase of ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores OR who experienced CIDP worsening (defined as a ≥8 kPa decrease in the hand grip strength in the more affected hand) OR ≥4 points decrease in raw summed Rasch-built Overall Disability Scale (R-ODS) score relative to the pre-SC treatment baseline score (at the time of withdrawal from the SC treatment period).
2. Time to relapse.
3. Change from pre-SC treatment baseline in R-ODS.

Safety

1. Number (percentage) of subjects experiencing any treatment-emergent serious and/or nonserious adverse events (SAEs and/or AEs, respectively), regardless of causality.
2. Number (percentage) of subjects experiencing causally related SAEs and/or AEs.
3. Number (percentage) of subjects with serious and/or nonserious adverse reactions (ARs) plus suspected ARs (SARs).

4. Number (percentage) with treatment-emergent SAEs and/or AEs associated with infusions, regardless of causality.
5. Number (percentage) of causally related SAEs and/or AEs associated with infusions.
6. Number (percentage) of AEs temporally associated with infusions (defined as AEs occurring during or within 72 hours after completion of an infusion).
7. Number (percentage) of serious and/or nonserious ARs plus suspected ARs associated with infusions.
8. Number (percentage) of treatment-emergent systemic AEs associated with infusions.
9. Number (percentage) of treatment-emergent local infusion site reactions associated with infusions.
10. Number and proportion of infusions for which the infusion rate was reduced and/or the infusion was interrupted or stopped due to intolerability and/or AEs.
11. Rates of systemic and local AEs, regardless of causality, expressed as number of events per infusion, per subject, and per subject-year.
12. Rates of causally related systemic and local AEs, expressed as number of events per infusion, per subject, and per subject-year.
13. Rates of systemic and local ARs plus suspected ARs, expressed as number of events per infusion, per subject, and per subject-year.
14. Number of subjects who have developed binding and/or neutralizing antibodies to rHuPH20.

Tertiary endpoints

Efficacy

1. Change from pre-SC treatment baseline in adjusted INCAT disability score.
2. Change from pre-SC treatment baseline in hand grip strength score.
3. Change from pre-SC treatment baseline in functional impact on everyday tasks as measured by R-ODS subcomponents.
4. Change from pre-SC treatment baseline in Medical Research Council (MRC) sum score.
5. Change from prescreen baseline in the total number or appearance of new DAs on EDX studies.

Patient-reported outcomes

1. Change from pre-SC treatment baseline in Short Form-36 (SF-36).
2. Change from pre-SC treatment baseline in European quality of life 5 dimensions (EQ-5D) scores.
3. HRU (such as days off school/work, unscheduled doctor visits, hospitalization, and emergency room [ER] visits).
4. Treatment satisfaction
5. Treatment preference.
6. PGIC.

Other

1. Serum trough IgG levels.

Sample size

The original planned sample size of 174 randomized subjects was estimated on the basis of the treatment effect in relapse rate of 13% and 45% observed in the GAMUNEX-C pivotal (ICE) study (Hughes et al., 2008) and an assumed remission rate of 45% (Viala et al., 2010).

The IVIg-experienced subjects enrolled into this study were not be withdrawn from IgG therapy prior to entering into the study. Thus, for sample size calculations, it was conservatively assumed that 45% of subjects on long-term IgG therapy no longer need therapy (which is termed "remission rate"). As such, a lower proportion of subjects (active treatment group: 13% x [1-0.45] = 7%, and placebo treatment group: 45% x [1-0.45] = 25%) was expected to relapse when withdrawn from their prior IVIg treatment in this study than the proportion of subjects who relapsed in the ICE trial (13% and 45% for IVIg and placebo groups, respectively). Therefore, the difference in the relapse rates between the HyQvia and placebo groups was estimated to be 18%. A sample size of 74 evaluable subjects per group (a total of 148 evaluable subjects) would provide approximately 80% power to detect a difference in relapse rates of 18% at a 5% significance level.

Based on additional information provided by more recent scientific literature, within amendment 6 the original sample size assumptions were no longer considered to be relevant and a larger treatment difference in relapse rates of 29% was expected. The percentage of subjects on long-term IgG therapy that no longer need therapy (the "remission rate") has been revised from 45% to 19% based on a random effects meta-analysis. Moreover, the assumed relapse rates were revised based on the point estimates from the random effect meta-analyses to 12% for HyQvia and 48% for placebo. Applying a correction factor to account for the expected remission rate of 19%, relapse rates were estimated to be 10% for the HyQvia treatment group and 39% for the placebo treatment group. Therefore, the difference in the relapse rates between the HyQvia and placebo groups was expected to be 29%, where a sample size of 120 randomized and dosed subjects (60 subjects per group) would provide 90% power. This power estimate was based on a continuity-corrected chi-squared test, equal allocation, a 15% drop-out rate, a two-sided 5% significance level and a difference in relapse rates of 29% and was derived based on 100,000 simulation runs and with dropouts imputed as no relapse, as per the planned primary analysis.

Randomisation

Subjects meeting all eligibility criteria (including baseline INCAT assessment) were randomly assigned to one of two SC treatment regimens (HyQvia or 0.25% albumin placebo with rHuPH20) at a ratio of 1:1. Randomisation codes were planned to be generated by the sponsor or the sponsor's representatives, and maintained by a centralised randomisation service.

Blinding (masking)

Epoch 1 of the study was double-blinded. Treatment assignments were not revealed to the subject, the investigator, site personnel, or the Sponsor/Sponsor's representative, except for intentionally unblinded study personnel.

Unblinded personnel were responsible for maintaining unblinded records in a secure, access-controlled location/system. To avoid inadvertent unblinding, results of serum IgG levels obtained after exposure to IP(s) were withheld from the subject, the investigator, site personnel, the Sponsor/Sponsor's representative, and all other blinded study personnel until all subjects had completed participation in Epoch 1. Any subject who completed Epoch 1, or discontinued prematurely from Epoch 1, irrespective of reason, was considered to have completed participation in Epoch 1.

Statistical methods

Analysis Populations/Sets

Modified intent-to-treat analysis set (MITT): The MITT analysis set included all randomised subjects who received any study treatment; this was the primary efficacy analysis set for Epoch 1 data. Analyses based on the MITT analysis set used the Epoch 1 planned (ie, as randomised) treatment.

Per protocol (PP) analysis set: The PP analysis set included all randomised subjects who received any study treatment and had no major or critical protocol deviations during Epoch 1 that may have had a significant impact on the primary outcome measure. The PP analysis set was used for sensitivity and/or supportive analyses.

Primary Endpoint(s) / Primary Estimand(s)

Primary endpoint: Relapse rate (proportion of subjects who experience a worsening of functional disability defined as an increase of ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores).

The primary analysis is a comparison of relapse rates in the two treatment groups, using a continuity-corrected chi-square test conducted at the 5% level of statistical significance (two-sided), and with missing outcomes imputed as no relapse. The estimated relapse rates are presented for each planned treatment group, along with the 95% CI computed using the Wilson score method.

Supplementary Analyses for Primary Endpoint

Sensitivity analyses to assess the robustness of inferences from the Epoch 1 primary analysis relating to imputing missing as "no relapse" are addressed in sensitivity analyses 1 and 2, and sensitivity analyses to assess the robustness of inferences from the Epoch 1 primary analysis relating to protocol deviations and the requirement for a confirmatory INCAT assessment is addressed in sensitivity analyses 3 and 4, respectively:

1. MITT analysis set with missing outcome in subjects who participated in Epoch 1 imputed as a relapse,

2. MITT Observed Cases analysis with missing outcome in subjects who participated in Epoch 1 excluded,

3. PP analysis set with missing outcome in subjects who participated in Epoch 1 imputed as no relapse,

4. MITT analysis set with missing imputed as no relapse, where relapse is alternatively defined as an increase in adjusted INCAT disability score of ≥1 point relative to the pre- SC treatment baseline score, on a single INCAT assessment; this sensitivity analysis removes the requirement for the increase by ≥1 point relative to the pre-SC treatment baseline score to be confirmed at a secondary confirmatory INCAT evaluation (to be performed as early as the same day of the first INCAT evaluation and no later than 7 days afterwards) in order to classify a subject as having relapsed.

As for the primary analysis, a continuity-corrected chi-square test is used to compare relapse rates between treatment groups for these sensitivity analyses.

Post-hoc sensitivity analyses

Two additional sensitivity analysis of the primary endpoint (in the MITT analysis set with missing relapse determinations in 8 subjects) were performed to assess the impact of subjects with missing relapse determination:

- an imputation under the MAR premise using multiple imputation for placebo and HyQvia
- a multiple Imputation Tipping Point Analysis imputed under MAR for Placebo and under MNAR for HyQvia

Secondary Endpoints / Secondary Estimand(s)

Secondary endpoints:

1. Proportion of subjects who experience a worsening of functional disability defined as one or more of the following: an increase of ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores; who experience CIDP worsening (defined as a ≥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 the time of withdrawal from the SC treatment period)

2. Time to relapse

3. Change from pre-SC treatment baseline in R-ODS

All Epoch 1 secondary efficacy endpoint analyses are based on the MITT analysis set.

1. This endpoint is analysed using a continuity-corrected chi-square test approach, as described for the Epoch 1 primary analysis, with no imputation of missing values. Additionally, the number and percentage of subjects meeting each component of worsening is presented.

2. Time to relapse is compared between treatment groups using the Wilcoxon survival test (i.e., Gehan's generalized Wilcoxon survival test). For subjects who relapsed in Epoch 1, time to relapse is calculated as: date of relapse – date of initial dose of IP in Epoch 1 + 1. Subjects who did not relapse in Epoch 1 will be censored with time to censoring calculated as: date of Epoch 1 discontinuation/completion – date of initial dose of IP in Epoch 1 + 1.

3. The change in ADL (R-ODS) from baseline to the end of the treatment period is analyzed using an analysis of covariance (ANCOVA) model to test the treatment effect, with baseline R-ODS score as a covariate. The last non-missing change in Epoch 1 is used for subjects who discontinued early. For subjects with no post-baseline R-ODS data, no imputation of post-baseline data was conducted and these subjects did not contribute to the analysis.

Multiplicity

No multiplicity adjustment is applied.

Subgroup Analyses

A comparison of relapse rates between planned treatment groups in the MITT analysis set using the methods described for the Epoch 1 primary analysis are conducted for the following subgroups: Age group (≤55 years, >55 years), Sex (Female, Male), Race (White, Black or African American, Asian, Native Hawaiian or Other Pacific Islander, American Indian or Alaska Native, Other, Not reported), Dosing regimen (2 weeks, 3 weeks, 4 weeks), Geographic region (North America, South America, Europe).

<u>Key changes in the Planned Analyses</u>

The changes defined in the SAP to the protocol-specified analyses were as follows:

• For the Epoch 1 MMRM analysis of R-ODS, a treatment-by-time interaction term was added to the model. Additionally, a plot of estimated means for the MMRM was added. Note: This analysis was only to be conducted if the discontinuation rates between arms were to be statistically significantly different.

• Subgroup analyses for the Epoch 1 and Epoch 2 primary endpoints were added to assess for exploratory evidence of a differential treatment effect across key subgroups.

The following additional analyses were not specified in the protocol or SAP:

• An "Overall" time point for R-ODS centile and alternative R-ODS centile scores by timepoint was added to the summary of observed values and changes from pre-SC treatment baseline to assess the overall change since subjects who relapsed or dropped out would not complete the weekly assessment following

relapse or drop out. Overall was derived as a per-subject mean of the available data from all postbaseline time points.

• Additional post-hoc sensitivity analyses based on the MITT analysis set were performed to assess the impact of subjects who had missing relapse determinations as well as the impact of subjects who discontinued early without confirmed relapse on the comparison of relapse rates.

At the CHMP request, the primary analysis was re-performed according to the strategies for the ICEs provided in Error! Reference source not found. including handling of missing values included in **Table 11.**

Table 11 Primary Estimand with Adequately Defined Intercurrent Events

Study Objective	To evaluate the efficacy of HYQVIA/HyQvia as a maintenance therapy for CIDP to prevent relapse of neuromuscular disability and impairment.	
Target population	Adults with CIDP.	
Analysis variable	Occurrence of relapse defined as worsening of functional disability defined as an increase of ≥1 point relative to the pre-treatment baseline score in 2 consecutive adjusted INCAT disability scores (where the second INCAT can be performed as early as the same day of the first INCAT and no later than 7 days after the first INCAT) within the observational period defined as • For 2 weeks dosing regimen: complete study to Week 27 • For 3 weeks dosing regimen: complete study to Week 26 • For 4 weeks dosing regimen: complete study to Week 28	
Treatment	HYQVIA/HyQvia and placebo administered at the subject's pre-randomization monthly equivalent dose (or at matching infusion volume for subjects in the placebo group) when administered at a dosing frequency of every 2, 3, or 4 weeks	
Intercurrent event and strategy	Randomized and did not receive study treatment (n=1 with placebo and n=5 with HYQVIA)	Hypothetical strategy envisioning that this ICE would not have occurred under the MCAR premise
	Use of prohibited concomitant medication	Treatment policy strategy (ie, difference in proportions of subjects who experienced a relapse regardless of whether subject used concomitant medication)
	Treatment non-adherence not leading to treatment discontinuation in Epoch 1	Treatment policy strategy (ie, difference in proportions of subjects who experienced a relapse regardless of whether subjected adhered to the planned treatment schedule not leading to treatment discontinuation in Epoch 1) Subjects who withdraw permanently from treatment are not followed up for their scheduled End-of-Epoch 1 visit and are addressed in the ICEs "Treatment discontinuation from Epoch 1 due to CIDP worsening" and "Treatment discontinuation from Epoch 1 due to other reasons than CIDP worsening").
	Treatment discontinuation from Epoch 1 due to CIDP worsening HyQvia n= 2 ([redacted] and [redacted]) Placebo: n=0	Composite strategy by combining the outcome of the variable of interest with discontinuation by using "relapse" for those subjects at day of early termination
	Treatment discontinuation from Epoch 1 due to other reasons than CIDP worsening	Hypothetical strategy envisioning that this ICE would not have occurred under the censoring at random (CAR) premise

	HyQvia n= 6 [redacted]) Placebo: n=2 ([redacted])	
Population level summary	Difference in proportions of subjects who experienced a relapse between HYQVIA/HyQvia and Placebo during the observational period	
Estimator	Maximum likelihood estimator for the difference in proportions and the corresponding two-sided 95% CI assuming binomially distributed occurrences of relapses within each arm	
Estimate	Numerical result of the estimator based on data of the "All Randomized Set"	

CAR=censoring at random; CI=confidence interval; CIDP=chronic inflammatory demyelinating polyradiculoneuropathy; INCAT=inflammatory neuropathy cause and treatment disability scale; ICE=intercurrent events; MCAR=missing completely at random; MITT=modified intent to treat.

Table 12 Event Probabilities for Subjects with Missing Values for the Primary Analysis

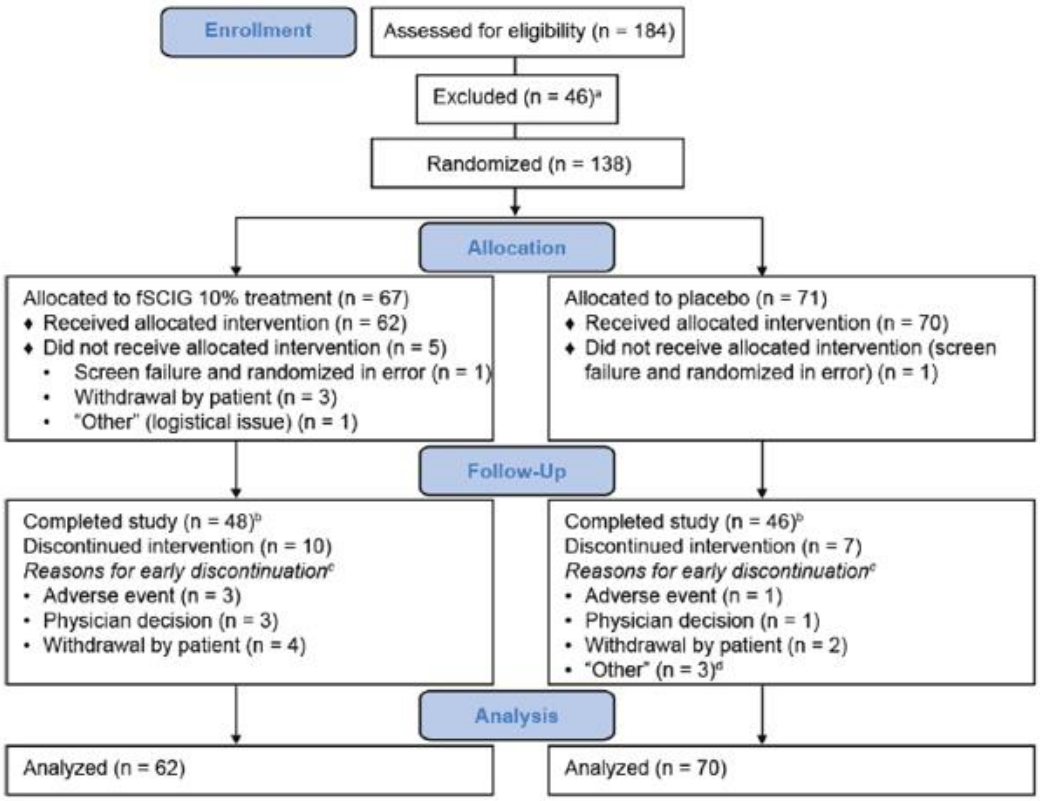
Subject	Treatment	Status	Details	P(relapse) at event day
[redacted]	HyQvia	INCAT >1 to baseline at day 94 with no confirmatory INCAT within 7 days and early termination after day 94	Withdrawal by subject: Subject feels he is worsening and does not want to continue.	Addressed in the ICE Treatment discontinuation from Epoch 1 due to CIDP worsening
[redacted]	HyQvia	INCAT >1 to baseline at day 191 with no confirmatory INCAT within 7 days and no early termination	Increase in INCAT confirmed at day 200 but outside the pre-specified window for confirmatory assessment (end of Epoch 1 was day 191 which was the day where an increase in INCAT was observed).	100% at day 191
[redacted]	Placebo	INCAT >1 to baseline at day 120 with no confirmatory INCAT within 7 days and no early termination	NTF available indicating no relapse at day 120. Subject completed Epoch 1 without any indication of relapse after day 120. End of Epoch 1 was day 191.	0% at day 120
[redacted]	HyQvia	INCAT >1 to baseline at day 188 with no confirmatory INCAT within 7 days and no early termination	NTF available indicating no relapse at day 188. Subject completed Epoch 1 without any indication of relapse after day 188. End of Epoch 1 was day 209.	0% at day 188
[redacted]	HyQvia	INCAT >1 to baseline at day 190 with no confirmatory INCAT within 7 days and no early termination	NTF available indicating no relapse at day 190. Subject completed Epoch 1 without any indication of relapse after day 190. End of Epoch 1 was day 192.	0% at day 190
[redacted]	Placebo	INCAT >1 to baseline at day 105 with no confirmatory INCAT within 7 days and no early termination	NTF available indicating no relapse at day 105. Subject completed Epoch 1 without any indication of relapse after day 105. End of Epoch 1 was day 189.	0% at day 105
[redacted]	HyQvia	No post-baseline INCAT and early termination after day 53	Withdrawal by subject: Progressive worsening since the study begun, thus patient indicated he did not want to continue receiving study drug, nor be contacted for study related things.	Addressed in the ICE Treatment discontinuation from Epoch 1 due to CIDP worsening
[redacted]	HyQvia	No post-baseline INCAT and early termination after day 22	Subject had AEs	Addressed in the ICE Treatment discontinuation from Epoch 1 due to other reasons than CIDP worsening

AEs=adverse event; CIDP= chronic inflammatory demyelinating polyradiculoneuropathy; ICE=intercurrent events; INCAT=inflammatory neuropathy cause and treatment disability scale; NTF=note to file.

Results

Participant flow

Figure 4 Participant Flow Chart for Study 161403



CIDP=chronic inflammatory demyelinating polyradiculoneuropathy; fSCIG=facilitated subcutaneous immunoglobulin INCAT=Inflammatory Neuropathy Cause and Treatment; IVIg=intravenous immunoglobulin.
[a] Patients were excluded for not meeting inclusion criteria (n=21) for the following reasons: did not meet diagnosis criteria (n=4); did not meet prior treatment criteria (n=5); did not meet INCAT disability score criteria (n=5); unwilling/unable to comply with protocol requirements (n=7). Patients were also excluded for meeting exclusion criteria (n=25) for the following reasons: presence of disease potentially affecting assessment n=2); presence/history of exclusionary conditions/infections (n-14); hypersensitivity/allergy to study treatments (n=3); abnormal laboratory values (n=4); treatment with corticosteroids within 8 weeks of screening (n=1); condition judged to impede participation/pose patient risk/confound study results (n=1).
[b] Patients who relapsed and entered Epoch 2 were not included in the number of patients who completed Epoch 1, nor in the number of patients who discontinued early from Epoch 1.
[c] CIDP relapse per protocol definition was recorded as the reason for early discontinuation under the following categories: fSCIG 10% treatment arm - physician decision (n=2); placebo arm - physician decision (n=1), withdrawal by patient (n=1), "other" (n=3).
[d] 2 patients relapsed per protocol definition and decided not to enroll in Epoch 2; 1 patient relapsed per protocol definition and did not enroll in Epoch 2 because of "sponsor decision: protocol deviation" (patient used IVIg outside of study).
Source: (Bril et al. 2023).

Recruitment

A total of 184 subjects were screened (enrolled), of which 46 (25%) were screen failures, 138 (75%) were randomised (including 2 screen failures who were randomised in error and 4 subjects who withdrawn prior to receiving the first dose of study drug), and 132 (95.7%) were dosed with IP. Of the 184 enrolled subjects, 18 were re-screened and received treatment dose, and therefore are not included in the screen failure count. All 132 dosed subjects were analysed for safety and efficacy, and included in the MITT and safety analysis sets; 94 subjects (excluding relapses and dropouts) completed Epoch 1.

Ninety-four subjects (71.2%) completed Epoch 1 and 17 subjects (12.9%) discontinued early from the study during Epoch 1. Ten out of the 132 subjects discontinued without relapse (dropped out) while 7 developed a relapse but did not wish to enrol in Epoch 2. A total of 21 subjects (15.9%) entered Epoch 2. All subjects in Epoch 2 successfully completed the study (no dropouts). There was no statistically

significant difference in overall discontinuation rates between HyQvia (16.1%, 10 subjects) and placebo (10%, 7 subjects) treatment (p=0.4302) and in time to discontinuation (p=0.215).

Table 13 Subject Disposition in Epoch 1 (Epoch 1 Enrolled Subjects)

Disposition	Placebo n (%)	HYQVIA n (%)	Total n (%)
Enrolled [a]			184
Screen failure [a]			46 (25.0)
Not screen failed and not randomized [b]			0
Subjects randomized [b]	71	67	138 (75.0)
Subjects randomized and dosed with IP (Epoch 1 MITT Set) [c]	70 (98.6)	62 (92.5)	132 (95.7)
Subjects dosed with IP (Epoch 1 Safety Set) [c]	70 (98.6)	62 (92.5)	132 (95.7)
Subjects who completed the study during Epoch 1 [d]	46 (65.7)	48 (77.4)	94 (71.2)
Subjects who discontinued early from study during Epoch 1 [d]	7 (10.0)	10 (16.1)	17 (12.9)
Primary Reason for early discontinuation [d]			
Adverse Event	1 (1.4)	3 (4.8)	4 (3.0)
Death			0
Lost to follow up			0
Physician decision	1 (1.4)	3 (4.8)	4 (3.0)
Study terminated by sponsor			0
Withdrawal by subject	2 (2.9)	4 (6.5)	6 (4.5)
Other	3 (4.3)		3 (2.3)
Subjects who Entered Epoch 2 [d]	17 (24.3)	4 (6.5)	21 (15.9)

IP = Investigational Product. MITT = Modified Intent-to-Treat analysis set. E1 = Epoch 1. E2 = Epoch 2.
The Enrolled Set consists of all subjects who signed the informed consent.
Subjects randomized includes 2 Subjects who screen failed and were randomized in error.
[a] Out of the unique 184 enrolled subjects, 18 subjects failed the first screening but succeeded in re-screening and received treatment dose and therefore are not included in the screen failure count.
[b] Number of subjects enrolled is the denominator used to calculate the percentage.
[c] Number of subjects randomized is the denominator used to calculate the percentage.
[d] Number of subjects dosed with IP is the denominator used in calculating percentages.
Subjects who relapsed and entered E2 are not included in the number of subjects who completed E1 nor number of subjects who discontinued early from study during E1.

Conduct of the study

Protocol deviations (PDs)

A total of 507 subject-level PDs were documented in 113 subjects for Epoch 1 during the study; these were reported across 50 study sites. Among the 507 PDs, 56 were critical PDs and included laboratory assessment criteria (n=22) and issues with conducting study procedures (n=18) and visit schedules (n=12). Of the total 507 PDs reported, 195 were major PDs and 256 were minor PDs. Major PDs included deviations from study procedures criteria (n=72), laboratory assessment criteria (n=44) and visit schedule criteria (n=29). Minor PDs included study procedures criteria (n=129) and visit schedule criteria (N=52).

Of the total 507 PDs reported in Epoch 1, 14 were considered related to COVID-19 and were reported across 6 sites. Among these 14 PDs, 7 were major PDs and 7 were minor PDs; no critical PDs were reported.

Baseline data

Overall, over half of the subjects were male (56.1%), White (92.4%) and not Hispanic or Latino (70.5%), with a mean age of 54.4 years. Slightly more than half of subjects (51.5%) were >55 years of age. There were no Black or African American or Asian subjects, 3 subjects (2.3%) were American Indian or Alaska Native, and 1 subject (0.8%) was classified as other; race was not reported for 6 subjects (4.5%). Overall, mean weight was 82.39 kg, mean BMI was 27.96 kg/m2, and approximately 70% of subjects were overweight (40.2%) or obese (29.5%). (see **Table 14**)

Overall, 85.2% and 99.8% of the planned and scheduled doses, respectively, were administered as expected, and 99.9% of the administered doses were within ±10% of the planned dose.

Table 14 Demographic and Other Screening Characteristics (Epoch 1 Safety Analysis Set)

Demographic Characteristic	Statistic	Placebo (N = 70)	HYQVIA (N = 62)	Total (N = 132)
Age (years)	n	70	62	132
	Mean (SD)	53.9 (13.42)	55.0 (14.26)	54.4 (13.78)
	Median	54.0	56.5	56.0
	Min, Max	27, 84	19, 86	19, 86
Age Group [n (%)]	≤ 55 years	36 (51.4)	28 (45.2)	64 (48.5)
	>55 years	34 (48.6)	34 (54.8)	68 (51.5)
Sex [n (%)]	Male	38 (54.3)	36 (58.1)	74 (56.1)
	Female	32 (45.7)	26 (41.9)	58 (43.9)
Race [n (%)]	White	64 (91.4)	58 (93.5)	122 (92.4)
	Black or African American	0	0	0
	Asian	0	0	0
	Japanese	0	0	0
	Non-Japanese	0	0	0
	Native Hawaiian or Other Pacific Islander	0	0	0
	American Indian or Alaska Native	2 (2.9)	1 (1.6)	3 (2.3)
	Other	0	1 (1.6)	1 (0.8)
	Not Reported	4 (5.7)	2 (3.2)	6 (4.5)
Ethnicity [n (%)]	Hispanic or Latino	14 (20.0)	9 (14.5)	23 (17.4)
	Not Hispanic or Latino	46 (65.7)	47 (75.8)	93 (70.5)
	Not Reported	10 (14.3)	6 (9.7)	16 (12.1)
Height (cm)	n	70	62	132
	Mean (SD)	171.9 (11.30)	171.0 (11.22)	171.4 (11.23)
	Median	170.0	171.0	170.0
	Min, Max	150, 194	150, 192	150, 194
Weight (kg)	n	70	62	132
	Mean (SD)	83.74 (21.373)	80.86 (16.206)	82.39 (19.105)
	Median	81.70	78.45	80.00
	Min, Max	55.0, 171.0	51.0, 130.0	51.0, 171.0
BMI (kg/m^2)	n	70	62	132
	Mean (SD)	28.25 (6.379)	27.63 (4.677)	27.96 (5.632)
	Median	27.60	27.00	27.15
	Min, Max	17.3, 57.1	17.5, 40.0	17.3, 57.1

BMI Category				
Underweight	n (%)	2 (2.9)	2 (3.2)	4 (3.0)
Normal	n (%)	17 (24.3)	19 (30.6)	36 (27.3)
Overweight	n (%)	30 (42.9)	23 (37.1)	53 (40.2)
Obese	n (%)	21 (30.0)	18 (29.0)	39 (29.5)

BMI = Body Mass Index. Max = Maximum. Min = Minimum. SD = Standard deviation.
IP = Investigational Product.
Epoch 1 Safety Analysis Set includes Epoch 1 Enrolled Subjects who received any double-blind IP.
The denominator for percentages is the number of subjects within the treatment group in the Epoch 1 Safety Analysis Set.
BMI Categories in kg/m^2: Underweight <18.5, Normal 18.5 to <25, Overweight 25 to <30, Obese ≥30.

CIDP History at Screening

The mean age of subjects at first diagnosis of CIDP was 50.3 years (range: 18 to 81 years). Over half of the subjects were male (56.1%), White (92.4%) and not Hispanic or Latino (70.5%). The mean time since first CIDP symptoms at screening was 5.8 years (range: 0.2 to 29.2 years). Mean time since CIDP diagnosis was 4.1 years (range: 0.2 to 19.6 years).

Table 15 CIDP History at Screening by Treatment Group (Epoch 1 Safety Analysis set)

Parameter	Statistic	Placebo (N = 70)	HYQVIA (N = 62)	Total (N = 132)
Time Since First CIDP Symptoms (years)	n	69	62	131
	Mean (SD)	5.07 (4.143)	6.51 (6.382)	5.75 (5.349)
	Median	4.00	4.50	4.10
	Min, Max	0.5, 18.2	0.2, 29.2	0.2, 29.2
Time Since CIDP Diagnosis (years)	n	70	61	131
	Mean (SD)	3.75 (3.563)	4.49 (4.757)	4.09 (4.161)
	Median	2.40	2.00	2.30
	Min, Max	0.2, 13.6	0.2, 19.6	0.2, 19.6
Subject Age at First Diagnosis of CIDP (years)	n	70	61	131
	Mean (SD)	50.1 (14.04)	50.5 (13.90)	50.3 (13.92)
	Median	50.0	51.0	50.0
	Min, Max	21, 76	18, 81	18, 81
Dosing Schedule, n (%)	2 Weeks	0	2 (3.2)	2 (1.5)
	3 Weeks	9 (12.9)	5 (8.1)	14 (10.6)
	4 Weeks	61 (87.1)	55 (88.7)	116 (87.9)
Any IgG Product Used within 6 Months of E1 Screening	Yes	69 (98.6)	62 (100.0)	131 (99.2)
	Missing	1 (1.4)	0	1 (0.8)
Subject Usage of Plasma Exchange Product Within 6 Months Prior to Screening, n (%)	Yes	0	0	0
	No	70 (100.0)	62 (100.0)	132 (100.0)
Subject Usage of Corticosteroids Within 6 Months Prior to Screening, n (%)	Yes	7 (10.0)	7 (11.3)	14 (10.6)
	No	63 (90.0)	55 (88.7)	118 (89.4)

CIDP = Chronic Inflammatory Demyelinating Polyradiculoneuropathy. Max = Maximum. Min = Minimum.
SD = Standard Deviation. IP = Investigational Product.
Epoch 1 Safety Analysis Set includes Epoch 1 Enrolled Subjects who received any double-blind IP.
The denominator for percentages is the number of subjects within the treatment group in the Epoch 1 Safety Analysis Set.

Prior medications

All but 1 subject (99.2%, 131/132) had used IgG products within 6 months of screening in Epoch 1. Data on the use of IgG products was missing in one subject as it was not recorded in the database. There were no subjects who had received plasma exchange within 6 months prior to screening. The dosing schedule for the majority of subjects (87.9%, 116/132) was every 4 weeks.

Overall, 10.6% (14/132) of subjects had taken corticosteroids within 6 months prior to screening. There was 1 subject who received steroids within 8 weeks prior to screening as per the effective protocol version that allowed for the use of low dose corticosteroids (eg, ≤10 mg prednisolone/day). Protocol amendment 5 was updated to preclude the use of any systemic corticosteroids within 8 weeks prior to screening, regardless of dose and indication, as requested by the FDA.

Medical history

The most commonly (≥20 subjects) reported medical history by SOC was vascular disorders (46.2%, 61/132), followed by surgical and medical procedures (42.4%, 56/132), metabolism and nutrition disorders (40.9%, 54/132), infections and infestations (34.8%, 46/132), nervous system disorders (34.1%, 45/132), musculoskeletal and connective tissue disorders (31.8%, 42/132), gastrointestinal (GI) disorders (26.5%, 35/132), and psychiatric disorders (18.9%, 25/132).

Concomitant medications

The majority of subjects (89.4%, 118/132) used concomitant medications during the study. The most commonly reported concomitant medications in ≥20 subjects by medication name were paracetamol (27 subjects [20.5%]) and pregabalin (23 subjects [17.4%]). There were no subjects who took concomitant non-study immunoglobulin which was not allowed in Epoch 1.

Numbers analysed

	Placebo (N = 71)	HYQVIA (N = 67)	Total (N = 184)
All Randomized Subjects, n	71	67	138
Epoch 1 Safety Analysis Set, n (%)	70 (98.6)	62 (92.5)	132 (95.7)
Epoch 1 Modified Intent-to-Treat Analysis Set, n (%)	70 (98.6)	62 (92.5)	132 (95.7)
Epoch 1 Per Protocol Set, n (%)	59 (83.1)	50 (74.6)	109 (79.0)

Outcomes and estimation

Primary Efficacy Endpoint: Relapse Rate

The proportion of subjects who relapsed in Epoch 1 was 9.7% (6/62 subjects) for HyQvia and 31.4% (22/70 subjects) for placebo. There was a statistically significant difference in relapse rates between the treatment groups, indicating treatment with HyQvia was effective (treatment difference -21.8%; p=0.0045, 95% CI: -34.45, -7.94).

Table 16 Relapse Rates in Epoch 1, with Missing Outcomes Imputed as No Relapse (Epoch 1 MITT Analysis Set)

	Placebo (N = 70)	HYQVIA (N = 62)	Treatment Difference, % (HYQVIA – Placebo)	Test for Treatment difference (p-value) [d]
Subjects with missing relapse determination, n [a]	2	6		
Subjects who relapsed, n (%) [b]	22 (31.4)	6 (9.7)	-21.8	0.0045
95% CI [c]	21.76, 43.03	4.51, 19.55	-34.45, -7.94	

CI = Confidence interval. INCAT = Inflammatory Cause and Treatment. IP = Investigational Product.
MITT = Modified Intent-to-Treat. SC = Subcutaneous.
Relapse is defined as an increase of ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores obtained not more than 7 days apart.
Epoch 1 MITT analysis set includes all randomized subjects who received any double-blind IP.
[a] Relapse status was missing if a subject did not have a baseline INCAT, or did not have at least 1 post-dose INCAT or had missing confirmatory INCAT in the presence of an abnormal INCAT (≥1 point relative to the pre-SC treatment baseline) within 7 days.
[b] The denominator for percentages is the number of subjects within the treatment group in the Epoch 1 MITT Analysis Set.
[c] Two-sided 95% Wilson confidence interval for single proportions and two-sided 95% Newcombe confidence interval for difference between proportions expressed as percentage.
[d] The treatment groups were compared using a continuity-corrected chi-square test, conducted at the two-sided 5% level of significance.

Relapse rates were re-calculated with an appropriate strategy to handle intercurrent events and missing values (see **Table 17**) The proportion of subjects who relapsed in Epoch 1 was 15.5% for HyQvia and 31.7% for placebo. There was a statistically significant difference in relapse rates between the treatment groups, indicating treatment with HyQvia was effective (treatment difference -16.2%; 95% CI: -29.92, -1.27).

Table 17 Relapse Rates in Epoch 1, with Appropriate Strategy to Handle Intercurrent Events and Missing Values (Epoch 1: All Randomized set)

Analysis	Hazard Ratio (Placebo/HyQvia)	Placebo relapse rate (2-sided 95% CI)	HyQvia relapse rate (2-sided 95% CI)	Difference in relapse rates (HyQvia - Placebo) (2-sided 95% CI)[g]
Primary Analysis [a],[b],[c],[d]	2.39	31.7 (21.96, 43.39)	15.5 (8.36, 26.84)	-16.2 (-29.92, -1.27)
Sensitivity analysis to assess the robustness of inferences to departures of the MCAR premise for the ICE "Randomized and did not receive study treatment" against the CNAR premise [b],[c],[d],[e]	2.29	32.0 (22.21, 43.70)	16.3 (8.93, 27.88)	-15.7 (-29.53, -0.53)
Sensitivity analysis to assess the robustness of inferences to departures regarding the assigned probabilities of relapse for handling of missing data [a],[b],[c],[d],[f]	2.39	32.6 (22.63, 44.50)	16.0 (8.66, 27.69)	-16.6 (-30.59, -1.24)

[a] Hypothetical strategy for ICE "Randomized and did not receive study treatment" by excluding those subjects from the analysis assuming that their outcomes are MCAR.

[b] Composite strategy for ICE "Treatment discontinuation from Epoch 1 due to CIDP worsening" by using "relapse" at day of early termination as outcome.

[c] Hypothetical strategy for ICE "Treatment discontinuation from Epoch 1 due to other reasons than CIDP worsening", ie, envisioning a scenario in which this ICE would not occur and predict the outcome that would have been observed in this scenario assuming CAR.

[d] Treatment policy strategy for ICEs "Use of prohibited concomitant medication" and "Treatment non-adherence not leading to treatment discontinuation in Epoch 1", ie, the outcome is considered regardless of whether these ICEs occur or not.

[e] Unobserved data for the n=5 HyQvia and n=1 placebo subjects who were "Randomized and did not receive study treatment" were imputed with a 2-times higher hazard than with the remaining HyQvia and placebo subjects, respectively.

[f] Use of elevated probability of relapse for subjects with missing data (ie, estimated placebo relapse from the primary analysis instead of 0% for placebo subjects [redacted] and [redacted] and estimated HyQvia relapse rate from the primary analysis instead of 0% for HyQvia subjects [redacted] and [redacted]).

[g] A two-sided 95% confidence interval (CI) for the difference not containing the value 0 is equivalent to rejecting the null hypothesis of no difference against the two-sided alternative at the 5% level of statistical significance.

Multiple imputations performed based on 100,000 imputed data sets.

Secondary Efficacy Endpoints

- Proportion of Subjects who Experienced a Worsening of Functional Disability

The proportion of subjects who experienced a worsening of functional disability in Epoch 1 was 37.5% (21/56 subjects) for HyQvia versus 54.4% (37/68 subjects) for placebo. The difference between the treatment groups was marginal (treatment difference -16.9%; p=0.0896) yet is considered clinically relevant.

Table 18 Summary of Worsening of Functional Disability (Epoch 1 MITT Analysis Set)

	Placebo (N = 70)	HYQVIA (N = 62)	Treatment Difference, % (HYQVIA – Placebo)	Test for Treatment difference (p-value) [c]
Subjects with data	68	56		
Subjects who worsened, n (%) [a]	37 (54.4)	21 (37.5)	-16.9	0.0896
95% CI [b]	42.66, 65.70	26.01, 50.59	-33.02, 0.69	
Met INCAT component criterion, n (%) [a]	22 (32.4)	6 (10.7)		
Met Hand grip strength component criterion, n (%) [a]	17 (25.0)	8 (14.3)		
Met R-ODS component criterion, n (%) [a]	20 (29.4)	13 (23.2)		

CI = Confidence interval. CIDP = Chronic immune-mediated demyelinating polyradiculopathy.
INCAT = Inflammatory Cause and Treatment. IP = Investigational Product. MITT = Modified Intent-to-Treat.
R-ODS = Rasch-built Overall Disability Score. SC = Subcutaneous.
Worsening of functional disability is defined as an increase of ≥1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores OR who experience CIDP worsening (defined as a ≥8 kPa decrease in the Hand Grip Strength in the more affected hand) OR ≥4 points decrease in R-ODS relative to the pre-SC treatment baseline score (at the time of withdrawal from the SC treatment period).
Epoch 1 MITT analysis set includes all randomized subjects who received any double-blind IP.
[a] The denominator for percentages is the number of subjects with data in the treatment group in the Epoch 1 MITT Analysis Set.
[b] Two-sided 95% Wilson confidence interval for single proportions and two-sided 95% Newcombe confidence interval for difference between proportions expressed as percentage.
[c] The treatment groups were compared using a continuity-corrected chi-square test.
Raw R-ODS scores are used. Other tables continue to use centile R-ODS.

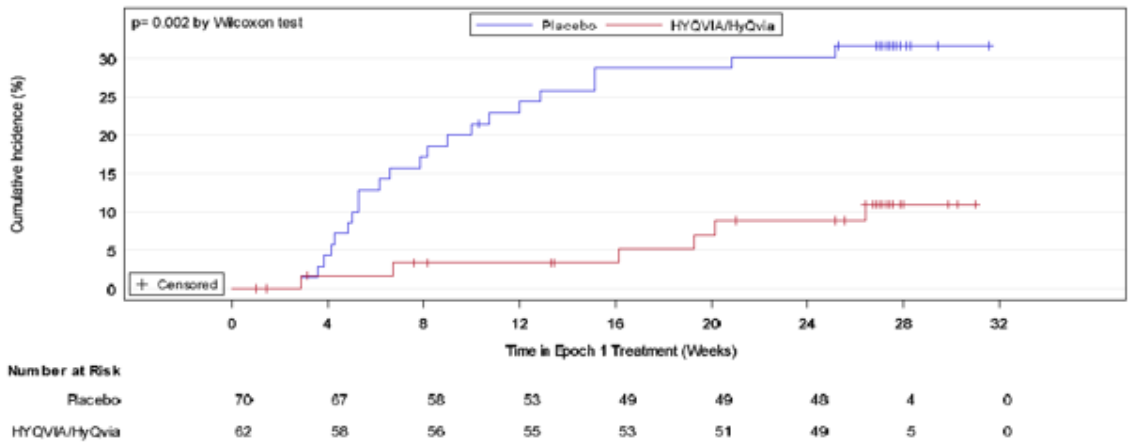
- Time to Relapse

Among HyQvia subjects (N=62), there were 6 subjects (9.7%) with events (relapsed) and 56 subjects (90.3%) who were censored (did not relapse in Epoch 1). Of the 56 subjects who were censored, 45 subjects (80.4%) completed Epoch 1, 5 subjects (8.9%) discontinued early from Epoch 1 without relapse, and 6 subjects (10.7%) had a missing relapse determination (2 with no post-baseline INCAT and 4 with missing confirmatory INCAT).

Among placebo subjects (N=70), there were 22 subjects (31.4%) with events and 48 subjects (68.6%) who were censored (did not relapse in Epoch 1). Of the 48 subjects who were censored, 44 subjects (91.7%) completed Epoch 1, 2 subjects (4.2%) discontinued early from Epoch 1 without relapse, and 2 subjects (4.2%) had a missing relapse determination (both subjects had missing confirmatory INCAT).

It was not possible to estimate median time to relapse because the censoring rate was high and fewer than 50% of subjects relapsed in either group. However, a Wilcoxon test indicated that overall, the time to relapse (days) was statistically significantly different between the treatment groups (p=0.002). Kaplan-Meier curves demonstrated early separation between the 2 groups at around Week 4, which is consistent with time course of the cessation of the effect of the last IVIg administered prior to the first IP dose. This finding further supports the effectiveness of HyQvia in maintaining the protective effect of IVIg in CIDP.

Figure 5 Kaplan-Meier Curves for Time to relapse by Treatment Group, with Missing Outcomes Imputed as No relapse (Epoch 1 MITT Analysis Set)



MITT = Modified Intent-to-Treat.
Curves estimated using the Kaplan-Meier method. Time to relapse is calculated as: date of relapse – date of initial dose of IP in Epoch 1 + 1. Subjects who did not relapse in Epoch 1 are censored with time to censoring calculated as: date of Epoch 1 discontinuation/completion – date of initial dose of IP in Epoch 1 + 1.
Epoch 1 MITT analysis set includes all randomized subjects who received any double-blind IP.

- Change from Pre-subcutaneous Treatment Baseline in R-ODS

  Analysis of change from pre-SC treatment baseline in R-ODS centile metric scores at EOE1T was conducted using ANCOVA. The least squares (LS) mean changes were -0.9 in the HyQvia group and -6.1 in the placebo group. The LS mean treatment difference of 5.2 was statistically significant (p=0.030) and the direction of the difference favoured HyQvia.

  Tertiary Endpoints

- Change from Pre-subcutaneous Treatment Baseline in Adjusted INCAT Disability Score

  For all dosing regimens combined, the mean change from pre-SC treatment baseline in adjusted INCAT disability score was -0.2 for HyQvia and 0.2 for placebo at EOE1T.

- Change from Pre-subcutaneous Treatment Baseline in Hand Grip Strength Score

  For all dosing regimens combined, the mean change from pre-SC treatment baseline in maximum grip strength score was 3.6 for the more affected hand (5.9 for HyQvia and 1.6 for placebo) and 2.1 for the less affected hand (5.2 for HyQvia and -0.6 for placebo) at EOE1T.

- Change from Pre-subcutaneous Treatment Baseline in Functional Impact on Everyday Tasks as Measured by R-ODS Subcomponents

  For all dosing regimens combined, the mean change from pre-SC treatment baseline in functional impact on everyday tasks as measured by alternative R-ODS centile metric scores was -0.8 for HyQvia and -1.8 for placebo at EOE1T.

- Change from Pre-subcutaneous Treatment Baseline in MRC Sum Score

  For all dosing regimens combined, the mean change from pre-SC treatment baseline in overall MRC sum score was 0.7 for HyQvia and -0.7 for placebo at EOE1T.

- Change from Pre-screen Baseline in the Total Number or Appearance of New Demyelinating Abnormalities on Electrodiagnostic Studies

  The mean total number of motor nerves studied per subject at Epoch 1 screening was 6.5 for HyQvia and 6.0 for placebo. The mean total number of motor nerves studied per subject at the end of the Epoch

1/exit as assessed by EDX tests was 6.5 for HyQvia and 6.4 for placebo. The mean total number of demyelinating findings decreased from 9.1 to 6.9 per subject in the HyQvia group and from 6.2 to 5.4 per subject in the placebo group at the end of Epoch 1/exit. The mean change was -2.5 for HyQvia and -1.1 for placebo. The mean total number of demyelinating findings per motor nerve decreased from 1.446 to 1.071 per subject in the HyQvia group and from 1.083 to 0.883 per subject in the placebo group at the end of Epoch 1/exit.

A total of 52 subjects in the HyQvia group and 57 subjects in the placebo group had baseline and exit data in the same nerve segments (matching nerve pairs). The mean number of new demyelinating findings per subject was similar between the HyQvia and placebo groups (1.5 and 1.4, respectively) at the end of Epoch 1/exit. However, the mean number of resolved demyelinating findings was higher in the HyQvia group (3.5 vs. 2.0).

Patient Reported Outcomes

- Change from Pre-subcutaneous Treatment Baseline in SF-36 Score

  SF-36 norm-based scores highlighted that both groups had poorer health than the general population as mean scores across all 8 domains at baseline were often less than 47. While no clinically meaningful changes in SF-36 domain and component scores were observed at EOE1T, when evaluating the change from baseline to EOE1T, the results demonstrated a greater trend of decline in most domains in the placebo group compared to HyQvia. Both the physical component score and mental component score showed decreases in the placebo group and increased scores in the HyQvia group.

- Changes from Pre-subcutaneous Treatment Baseline in EQ-5D Scores

  The proportion of subjects reporting greater disability across all domains of the EQ-5D dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) was higher for the placebo group compared to the HyQvia group at the end of treatment.

- Healthcare Resource Utilization

  Overall, 44.7% (59/132) of subjects used healthcare resources excluding planned doctor visits. Subjects reported a total of 86 unscheduled doctor visits, 46 ER visits, 68 hospitalizations, and 88 days off from work/school. Per subject-year rates were 1.66 and 1.36 and for unscheduled doctor visits, 0.99 and 0.63 and for ER visits, 1.59 and 0.80 for hospitalizations, and 2.04 and 1.04 for days off from school/work for HyQvia and placebo, respectively. Per subject-year rates were 0.14 and 0.28 for ER visits related to CIDP, and 0.95 and 0.59 for hospitalizations related to CIDP in the HyQvia and placebo groups, respectively.

- Treatment Satisfaction

  Responses to the TSQM-9 were obtained for 127 of 132 subjects at baseline. The overall mean TSQM-9 scores for medication at baseline were similar for the 2 groups. For the HyQvia group, the mean TSQM-9 scores at baseline (n=62) were 71.2, 67.1, and 55.7 for global satisfaction, effectiveness, and convenience, respectively. For the placebo group, the mean TSQM-9 scores at baseline (n=65) were 71.4, 64.7, and 59.1 for global satisfaction, effectiveness, and convenience, respectively.

  Responses on the TSQM-9 were obtained from 118 subjects at the EOE1T/early termination (ET). At EOE1T/ET, the median global satisfaction score was higher for the HyQvia group (71.4) than the placebo group (57.1). Similarly, the median effectiveness score was higher for HyQvia (66.7) than placebo (50), and the median convenience score between the 2 groups was the same (HyQvia, 66.7; placebo, 66.7).

- Treatment Preference

  The treatment preference questionnaire demonstrated a favourable overall preference to HyQvia compared to their pre-study treatment (IVIg), with 36 subjects (66.7%) who received HyQvia preferring the study medication compared to their pre-study treatment. A total of 45 subjects (83.3%) in the HyQvia group responded that they would choose to continue receiving the study drug. The majority of

subjects also found HyQvia more convenient than their pre-study treatment (38 subjects [70.4%]). Most subjects preferred the study drug in terms of "scheduling their treatment" and "convenience" with 59% and 67.6%, respectively.

- Patient Global Impression of Change

The responses to the PGIC questionnaire were obtained for 105 of 132 subjects (HyQvia 54 subjects; placebo, 51 subjects) at the EOE1T. Overall, at the EOE1T, 30.5% (32/105) of subjects reported they were minimally improved, 19% (20/105) of subjects reported they were much improved, and 3.8% (4/105) of subjects reported they were very much improved. The responses were similar for the HyQvia and placebo-treated subjects.

Other Analyses: Serum Trough IgG Levels

Mean baseline observed values were comparable between the HyQvia (1847.9 mg/dL) and placebo (1824.2 mg/dL) treatment groups. The Epoch 1 Week 1 (E1W1) observed values were comparable to the baseline values and between treatment groups (HyQvia, 1872.9 mg/dL; placebo, 1831.7 mg/dL). The E1W1 observed value may be the baseline value if it is the last nonmissing value before the first administration of IP. The E1INT observed values were lower than values reported at E1W1 for both treatment groups (HyQvia, 1473.9 mg/dL; placebo, 1129.2 mg/dL), and the mean value was higher in the HyQvia group than the placebo group. The EOE1T/ET values continued to remain stable for both treatment groups and as expected, the mean value was higher in the HyQvia group than the placebo group (HyQvia, 1528.4 mg/dL; placebo, 1244.4 mg/dL). The HyQvia observed values were higher at all visits compared to those reported for placebo.

Descriptive statistics of serum total trough IgG levels in Epoch 1 (MITT analysis set) after Day 120 or at the time of CIDP release are summarized in Table 18 by treatment group and overall (total).

Mean serum total trough IgG levels at time of relapse for subjects who developed a relapse were 1612.5 mg/dL for HYQVIA and 1455.4 mg/dL for placebo. Mean serum total trough IgG levels after Day 120 for subjects who did not develop a relapse were 1502.6 mg/dL for HyQvia and 1149.7 mg/dL for placebo.

Although trough IgG levels were higher in subjects who developed a relapse than in subjects who did not in the placebo group, there did not appear to be strong correlation between serum total trough IgG level and relapse for either treatment groups.

Ancillary analyses

Sensitivity analysis of the primary endpoint

A conservative sensitivity analysis where missing relapse determinations were imputed as relapse for the MITT analysis set supported the primary findings by demonstrating a clinically meaningful effect size. The HyQvia relapse rate (19.4%; N=62) was lower than the placebo relapse rate (34.3%; N=70), resulting in an observed treatment difference of -14.9%; (p=0.0842, 95% CI:-29.04, 0.33). Although this conservative sensitivity analysis did not reach statistical significance at the two-sided 5% level, the treatment difference of 14.9% still indicates a clinically meaningful advantage of HyQvia on relapse rate.

An observed case analysis conducted in the MITT analysis set, excluding 8 subjects with a missing relapse determination, demonstrated a statistically significant difference between the relapse rates of the HyQvia group (10.7%) and the placebo group (32.4%) (p=0.0080). The estimated treatment difference of -21.6% indicated that HyQvia was more effective than placebo in preventing relapse of CIDP.

Analysis of the primary endpoint conducted in the PP analysis set (HyQvia, N=50; placebo, N=59), with missing relapse determinations imputed as no relapse, demonstrated a statistically significant difference between the relapse rates of the HyQvia group (6%) and the placebo group (23.7%) (p=0.0228). The estimated treatment difference of -17.7% indicated that HyQvia was more effective than placebo in preventing relapse of CIDP. An analysis of relapse rates was conducted in the MITT analysis set, using the

alternative definition of relapse in Epoch 1 (no confirmatory INCAT required), with missing relapse determination imputed as no relapse. Using the alternative definition, the relapse rate in the HyQvia group (16.1%; N=62) was lower than the relapse rate in the placebo group (34.3%; N=70). The estimated treatment difference of -18.2% was statistically significant (p=0.0292) and the direction of the difference indicated that HyQvia was more effective than placebo in preventing relapse of CIDP.

Post-hoc sensitivity analyses

An additional sensitivity analysis of the primary endpoint in the MITT analysis set, with missing relapse determinations in 8 subjects imputed under the MAR premise using multiple imputation for placebo and HyQvia indicted a statistically significant difference in relapse rates of the HyQvia group (13.7%) and the placebo group (31.5%). The estimated difference in relapse rates was -17.8% (95% CI: -31.24%, -2.80%). The additionally performed tipping point analysis indicated that a nonstatistically significant result would require that the relapse rate for the N=6 subjects with missing relapse determination in the HyQvia arm is more than 5.5 times the relapse rate among the remaining N=56 subjects while keeping the relapse rate for the whole placebo group at 31.5% (ie, under MAR).

Additional sensitivity analyses were conducted in the MITT analyses set for subjects who terminated early without confirmed relapse or who had missing relapse determination. A complete case analysis excluding 8 subjects with a missing relapse determination and the 11 subjects who terminated early without confirmed relapse demonstrated a statistically significant difference between relapse rates of the HyQvia group (11.8%; N=51) and placebo group (33.3%; N=66). The estimated treatment different in relapse rates was -21.6% (95% CI: -35.11%, - 6.13%). The analysis using multiple imputation under the MAR premise for the N=15 subjects (HyQvia 11, placebo 4) who had missing relapse determinations or who terminated early without confirmed relapse indicated a nonstatistically significant difference in relapse rates of the HyQvia group (20.1%) and placebo group (33.0%). The estimated treatment difference in relapse rates was -12.9% (95% CI: -27.84%, 4.19%). The tipping point analysis indicated that a nonstatistically significant result would require that the relapse rate for the N=11 subjects who terminated early without confirmed relapse or had missing relapse determination with HyQvia is more than 2.75 times higher than the relapse rate among the remaining 51 subjects while keeping the relapse rate for the whole placebo group at 33% (ie, under MAR).

Subgroup analysis of the primary endpoint

Subgroup analyses of the primary endpoint was evaluated for age, sex, race, dosing regimen and geographic region.

Age:

treatment differences in age group ≤ 55 years: -14.3% (p=0.259) and > 55years -29.4% (p=0.010),

treatment-by-age group interaction p=0.402

Table 19 Subgroup Analysis: Summary and Analysis of Relapse Rates in Epoch 1 by Treatment Group and Age Group, with Missing Outcomes Imputed as No Relapse (Epoch 1 MITT Analysis Set)

	Placebo (N = 70)	HYQVIA (N = 62)	Treatment Difference, % (HYQVIA – Placebo)	Test for Treatment difference (p-value) [d]
Age Group <=55 YEARS				
Subjects, n	36	28		
Subjects who relapsed, n (%) [a]	9 (25.0)	3 (10.7)	-14.3	0.259
95% CI [b]	13.8, 41.1	3.7, 27.2	-31.8, 5.7	
Age Group >55 YEARS				
Subjects, n	34	34		
Subjects who relapsed, n (%) [a]	13 (38.2)	3 (8.8)	-29.4	0.010
95% CI [b]	23.9, 55.0	3.1, 23.0	-47.1, -9.3	
Treatment-by-Age Group Interaction [c]				
p-value				0.402

Sex:

treatment differences in male: -20,6% (p=0.049) and female -22,8% (p=0.087),

treatment-by-sex interaction p=0.910

Table 20 Subgroup Analysis: Summary and Analysis of Relapse Rates in Epoch 1 by Treatment Group and Sex, with Missing Outcomes Imputed as No Relapse (Epoch 1 MITT Analysis Set)

	Placebo (N = 70)	HYQVIA (N = 62)	Treatment Difference, % (HYQVIA – Placebo)	Test for Treatment difference (p-value) [d]
Male				
Subjects, n	38	36		
Subjects who relapsed, n (%) [a]	11 (28.9)	3 (8.3)	-20.6	0.049
95% CI [b]	17.0, 44.8	2.9, 21.8	-37.3, -2.6	
Female				
Subjects, n	32	26		
Subjects who relapsed, n (%) [a]	11 (34.4)	3 (11.5)	-22.8	0.087
95% CI [b]	20.4, 51.7	4.0, 29.0	-41.7, -0.5	
Treatment-by-Sex Interaction [c]				
p-value				0.910

Race:

This study included very few non-White subjects (N=3) and subjects of unknown race (N=7), so results for race should be interpreted with caution.

Treatment differences in white: -17.8% (p=0.025), American Indian or Alaska Native -100% (p=ND), not reported -50% (ND)

treatment-by-race interaction (p=0.825)

Dosing regimen:

Statistical analyses were not done for the 2-week and 3-week dosing regimens as the number of subjects was too small.

Treatment differences in every 2 weeks ND (p=ND), every 3 weeks -4,4% (p=ND) and every 4 weeks -20.4% (p=0.012)

Treatment- by-Dosing Regimen Interaction (p=0.648)

Geographic region:

Treatment differences in Europe -16.9% (p=0.070), North America -18.2% (p=0.669) and South America -62.5% (p=0.044)

Treatment- by-region Interaction (p=0.491)

Table 21 Subgroup Analysis: Summary and Analysis of Relapse Rates in Epoch 1 by Treatment Group and Geographic Region, with Missing Outcomes Imputed as No Relapse (Epoch 1 MITT Analysis Set)

	Placebo (N = 70)	HYQVIA (N = 62)	Treatment Difference, % (HYQVIA – Placebo)	Test for Treatment difference (p-value) [d]
Europe				
Subjects, n	51	48		
Subjects who relapsed, n (%) [a]	15 (29.4)	6 (12.5)	-16.9	0.070
95% CI [b]	18.7, 43.0	5.9, 24.7	-32.0, -0.7	
North America				
Subjects, n	11	7		
Subjects who relapsed, n (%) [a]	2 (18.2)	0 (0.0)	-18.2	0.669
95% CI [b]	5.1, 47.7	0.0, 35.4	-47.7, 19.6	
South America				
Subjects, n	8	7		
Subjects who relapsed, n (%) [a]	5 (62.5)	0 (0.0)	-62.5	0.044
95% CI [b]	30.6, 86.3	0.0, 35.4	-86.3, -14.8	
Treatment- by-Region Interaction [c]				
p-value				0.491

Subgroup analyses for the secondary endpoint "Worsening of Functional Disability" by age, sex and geographic region were also performed. For all subgroups, the treatment effect was similar to the main analysis with a higher proportion of placebo subjects experiencing worsening of functional disability.

Subgroup analyses for the secondary endpoint "Time to Relapse" by age, sex and geographic region were performed. For all subgroups, the time to relapse curves separated early by treatment group, similar to the main analysis.

Subgroup analyses for the secondary endpoint "Change from pre-treatment baseline in R-ODS score" by age, sex and geographic region were performed. For all subgroups, the treatment effect was similar to the main analysis with a greater decrease in least squares (LS) mean change from baseline in centile R-ODS score using ANCOVA in the placebo arm.

Some discrepancies between regions were noted and discussed by the MAH but were not considered conclusive due to the small sample size.

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22 Summary of Efficacy for trial 161403

Title: A Phase 3 Study to Evaluate the Efficacy, Safety, and Tolerability of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HyQvia) and Immune Globulin Infusion (Human), 10% (GAMMAGARD LIQUID/KIOVIG) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)		
Study identifier	161403	
Design	Study 161403 was a Phase 3, prospective, multicentre, double-blind, randomized, placebo -controlled study to evaluate the efficacy, safety, and tolerability of HyQvia and IGI (Human), 10% (GGL/KIOVIG) for the treatment of CIDP.	
	Duration of main phase:	Epoch 1 (SC treatment): up to 6 months Epoch 2 (IV treatment): 6 months
	Duration of Run-in phase:	Screening period up to 8 weeks
	Duration of Extension phase:	not applicable (study 161505)

Hypothesis	Superiority		
Treatments groups	HyQvia		HyQvia (subject's pre-randomisation monthly equivalent dose of IVIg). Up to 6 months, randomised n=62
	placebo		Placebo. Up to 6 months, randomized n=70
Endpoints and definitions	Primary endpoint		Relapse rate (proportion of subjects who experienced a worsening of functional disability defined as an increase of ⩾1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores obtained less than 7 days apart).
	Secondary endpoints		Epoch 1: worsening of functional disability, time to relapse, R-ODS, safety
	Tertiary endpoints		Epoch 1: INCAT, hand grip strength, patient-reported outcomes, MRC sum score, serum trough IgG levels
Database lock	23.2.22 (last subject completed)		

Results and Analysis Epoch 1

Analysis description	**Primary Analysis**			
Analysis population and time point description	MITT analysis set Up to 8 months			
Descriptive statistics and estimate variability	Treatment group	Placebo	HyQvia	
	Number of subject	70	62	
	Subjects who relapsed, n (%)	22 (31.4 %)	6 (9.7 %)	
	95% CI	21.76, 43.03	4.51, 19.55	

Effect estimate per comparison	Primary endpoint	Comparison groups	HyQvia vs placebo
		Difference in % CIDP relapse (or withdrawal)	-21.8 %
		95 % CI	-34.45, -7.94
		P-value	0.0045
Notes	Predefined sensitivity analyses and post-hoc sensitivity analyses confirmed primary analysis.		

Analysis performed across trials (pooled analyses and meta-analysis)

Relapse Rates (Primary Efficacy Endpoint)

Table 23 provides a summary of relapse rates in the HyQvia CIDP analysis set of Study 161403 Epoch 1 and Study 161505. During a 194.7 patient-years follow up period, a total of 10 subjects developed a relapse (10.0%). The 6-month relapse rate was 2.6%. The relapse rate was consistent across age (≤55 - >55 years) and gender.

Table 23 Summary of Subject Relapse Rates with Missing Relapse Determinations Imputed as No relapse (HYQVIA CIDP Analysis Set)

	HYQVIA/HyQvia
Subjects, n	100
Subjects with missing relapse determination, n(%)[a]	16 (16.0)
Subjects who relapsed, n (%)[b]	10 (10.0)
95% CI[c]	0.06, 0.17
6-month relapse rate	0.0257
Subject years of follow-up	194.66

Additional ad-hoc analysis where 16 subjects with missing relapse determination in the ISE set were imputed as relapse revealed a 6-month relapse rate of 7.4%. To provide context, the 6-month relapse rate in subjects treated with (IVIg) in the extension phase of the ICE trial was 13% (Hughes et al., 2008). In the PATH extension study, the relapse rate in subjects assigned to high dose SCIg was 10% during a 48-week follow-up period (corresponding to an approximately 5% relapse rate for 6 months) (van Schaik et al., 2019). Overall, the conservative estimate (by imputing missing relapse determination as relapse) for relapse rate observed in the HyQvia CIDP analysis set falls towards the lower end of the published range.

Time to Relapse

Overall, there were 10 (10%) of 100 subjects with events (relapsed) and 90 (90.0%) of 100 subjects who were censored (did not relapse as of data cut-off). Of the 90 subjects who were censored, 4 (4.0%) completed Study 161403 and did not enrol in Study 161505, 40 (40%) discontinued early from either study, and 46 (46.0%) were ongoing at time of the data cut-off. Time to relapse ranged from 7 to 1982 days. The Kaplan- Meier curve for time to relapse of the HyQvia CIDP analysis set is consistent with the results from each study and demonstrate the overall stable disease course in subjects treated with HyQvia.

Summary of Worsening of Functional Disability

Overall, 39% of the subjects met the worsening criteria. The 6-month worsening rate was 10%.

Worsening was defined by including dichotomous thresholds of ≥4 for decreases in the raw R-ODS score and ≥8 kPa decrease in the hand grip strength in the more affected hand compared to baseline. Such thresholds have not been validated as minimally important clinical differences. Unlike dichotomous analysis, the box plots for individual components of the composite score through the entire course of the study suggested that there was no apparent functional deterioration over time. R-ODS decrease ≥4 occurred in a total of 33 subjects, but in approximately half of the subjects (n=17), R-ODS reductions were discrete incidents and did not persist at the subsequent prescheduled assessment time point, suggesting incidental fluctuation rather than persistent worsening.

Table 24 Summary of Worsening of Functional Disability (HYQVIA CIDP Analysis Set)

	HYQVIA/HyQvia
Subjects, n	100
Subjects who worsened, n (%)[a]	39 (39.0)
95% CI[b]	0.30, 0.49
6-month worsening rate	0.1002
Subject-years of follow-up	194.66
Met INCAT component criterion	10 (10.0)
Met Hand grip strength criterion	19 (19.0)
Met R-ODS component criterion	20 (20.0)

Supportive study

Study 161505: Long-Term Tolerability and Safety of Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase (HyQvia) for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

This study was a Phase 3b, open-label, multicentre study to assess the long-term safety, tolerability, and immunogenicity of HyQvia (IGI, 10% with rHuPH20 administered subcutaneously) for maintenance therapy to prevent relapse. This study was an extension of Clinical Study 161403, a Phase 3 Efficacy, Safety, and Tolerability Study of HyQvia and GAMMAGARD LIQUID (GGL)/KIOVIG in CIDP.

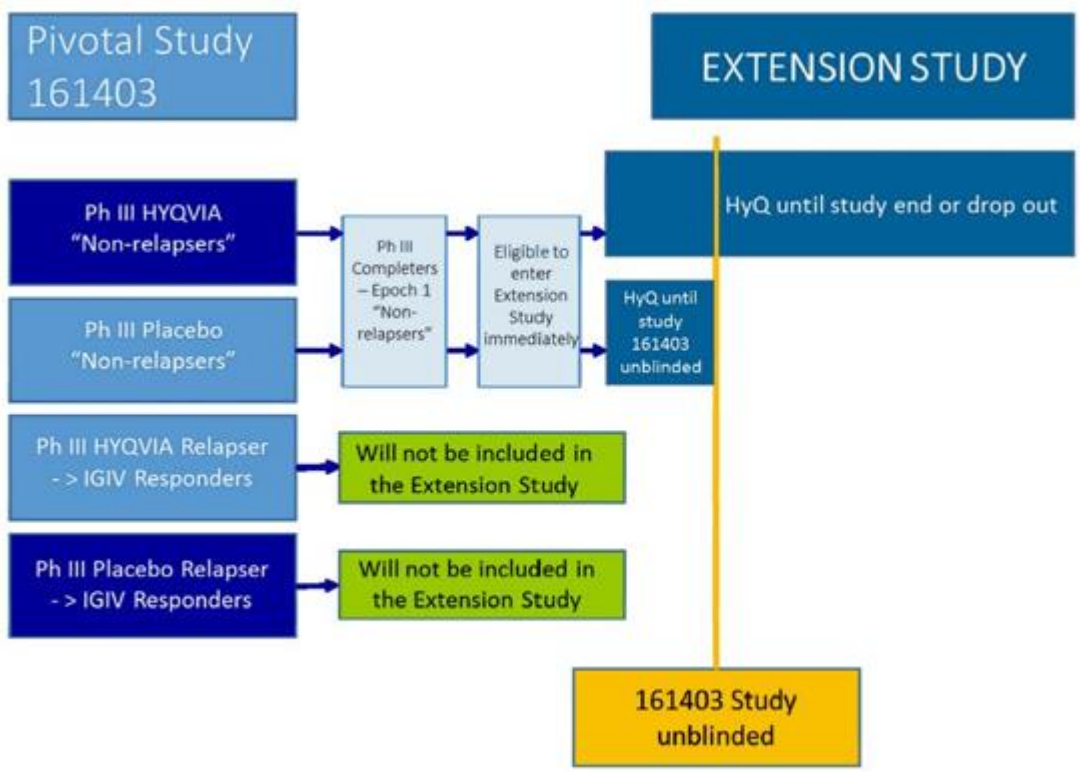
Methods

Study design

In this Extension Study, eligible subjects received HyQvia in an open-label fashion until relapse or until predetermined study end for the specific country from which the subject was participating. Enrolment into this study was open to subjects who completed Study 161403 Epoch 1 without CIDP worsening and who provided informed consent by signing an ICF. Subjects must have met all eligibility criteria in order to participate in this long-term Extension Study.

Enrolment into the Extension Study (signed informed consent) took place prior to or during the subject's study completion visit in Study 161403. The termination visit of Study 161403 was to serve as the baseline visit for the Extension Study. Subjects continued to receive the same dose and dosing regimen of HyQvia in the Extension Study as they received in Epoch 1 of the Phase 3b pivotal study (Study 161403). Subjects who were on placebo in Epoch 1 (Study 161403), received HyQvia treatment. The dosing range continued to be 0.4 g/kg to 2.4 g/kg given in a frequency of 2, 3 or 4 week intervals.

Figure 6 Study Design Schematic



Objectives

Primary Objective:

To evaluate the long-term safety, tolerability, and immunogenicity of HyQvia.

Exploratory Objectives

The exploratory objectives of this study were:

1. To assess the long-term effect of HyQvia on clinical outcome measures, including prevention of relapse, change in functional ability, hand grip strength, and muscle strength.
2. To assess the long-term effect of HyQvia on quality of life, health utility, health resource utilization (HRU), treatment satisfaction, treatment preference, and subject global impression of change.
3. To evaluate improvement in functional impact on everyday tasks as measured by a prespecified subscore of Rasch-built Overall Disability Scale (R-ODS).

Interim Analysis (IA)

An IA was performed based on a data snapshot taken on the same day as database lock of Study 161403 (Epoch 1). Data to be analysed descriptively at this IA were determined before unblinding of Study 161403. The main study team did not become unblinded to subject treatment due to any IA that was conducted prior to the Study 161403 (Epoch 1) database lock. The unblinded statistical team was not involved with study conduct or data cleaning decisions.

Participant flow

A total of 85 subjects met the selection criteria in Study 161505. As of the IA cut-off date, there were 6 subjects who had enrolled in Study 161505 but did not receive their first dose of IP. These 6 subjects were excluded. Study 161505 analyses included 79 subjects who were dosed with IP. Thirty-five subjects discontinued early (**Table 25**). The most common reason for early termination was CIDP. Other reasons included logistical issues to get infusions, medical conditions that required the use of medications that are not allowed by the protocol, COVID-19 related issues, and CIDP relapse.

Table 25 Subject Disposition (Enrolled Subjects)

Disposition	Placebo - HYQVIA/HyQvia [a] n (%)	HYQVIA/HyQvia - HYQVIA/HyQvia [b] n (%)	Total n (%)
Subjects from Study 161403 enrolled in Study 161505 [c]			86
Subjects who did not meet all selection criteria in Study 161505 [d]			1 (1.2)
Subjects who did not receive first dose of IP prior to IA cut-date [d]			6 (7.0)
Subjects dosed with IP [d]	38	41	79 (91.9)
Subjects who completed study [e]	0	0	0
Subjects who discontinued study early [e]	15 (39.5)	20 (48.8)	35 (44.3)
Subjects ongoing at data cut-off [e]	23 (60.5)	21 (51.2)	44 (55.7)
Reason for early discontinuation [e]			
Adverse event(s)	1 (2.6)	2 (4.9)	3 (3.8)
Death	1 (2.6)	0	1 (1.3)
Lost to follow up	0	0	0
Physician decision	4 (10.5)	11 (26.8)	15 (19.0)
Study terminated by sponsor	0	0	0
Withdrawal by subject	6 (15.8)	6 (14.6)	12 (15.2)
Unblinded subject chose not to participate in the next Visit	0	0	0
Other	3 (7.9)	1 (2.4)	4 (5.1)

Data Sets Analysed

The safety analysis set included all subjects who were enrolled in the Extension Study and who received at least one dose of study medication. This was the primary analysis set for all analyses unless otherwise specified. Descriptive analyses based on the Safety Set are presented by treatment received during Study 161403 Epoch 1.

A total of 79 (91.9%) subjects were included in the safety analysis set.

Results

Other Observations Related to Efficacy

The other exploratory endpoints (composite worsening outcome, change from baseline in functional impact on everyday tasks as measured by R-ODS sub-components, Patient-reported Outcomes [PROs] and Health Economics scales, and trough serum IgG levels) were not assessed in this IA and will be reported in the final CSR.

- Relapse Rate

A total of 63 out of 79 subjects were evaluable for CIDP relapse (i.e., they had no missing post-baseline INCAT assessments and/or no missing relapse assessment due to an elevated INCAT with no confirmatory INCAT within window). Analysis included 30 subjects in the Placebo – HyQvia treatment group and 33 subjects in the HyQvia –HyQvia treatment group. During 168.828 patient-years follow up period, a total of 5 subjects developed a relapse (7.9%), with a higher percentage in the HyQvia –HyQvia treatment group as compared with the Placebo –HyQvia treatment group (12.1% [4/33 subjects] versus 3.3% [1/30 subjects], respectively).

- Time to Relapse

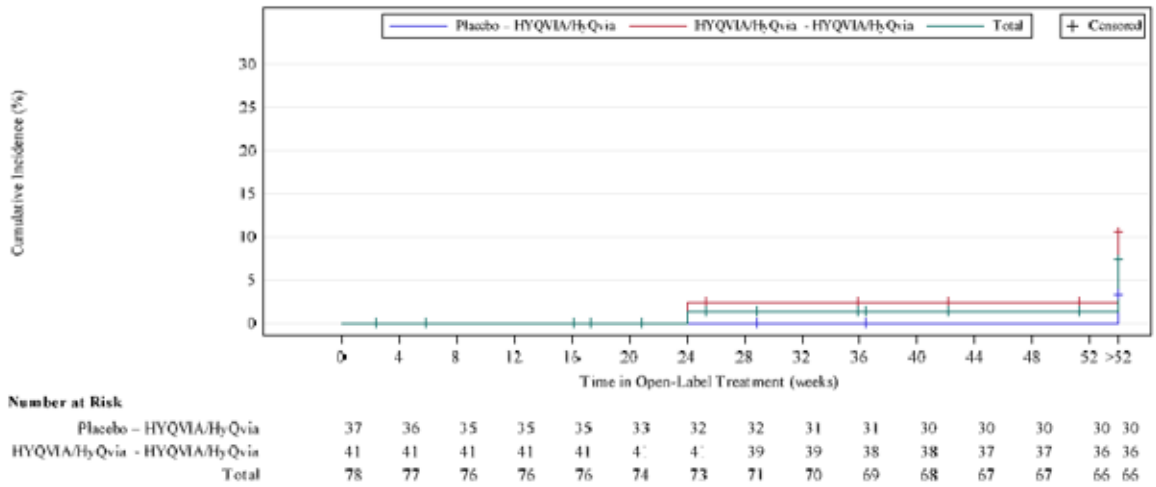
A Kaplan-Meier plot for time to relapse is presented in **Figure 7**. Overall, there were 5 (7.9%) of 63 subjects with events (relapsed) and 58 (92.1%) of 63 subjects who were censored (did not relapse as of data cut-off). Of the 58 subjects who were censored, 25 (43.1%) had early discontinuation from the study without relapse and 33 (56.9%) were ongoing at time of the IA data cut-off. The 6-month relapse rate was 1.5% in the overall population (Placebo –HyQvia: 0.7%; HyQvia - HyQvia: 2.1%).

Among subjects in the HyQvia –HyQvia treatment group, there were 4 (12.1%) subjects with relapse and 29 (87.9%) subjects who were censored (did not relapse as of data cut-off). Of the 29 subjects who were censored, 16 (55.2%) subjects were ongoing at data cut-off and 13 (44.8%) subjects discontinued early from the study without relapse.

Among subjects in the Placebo –HyQvia treatment group, there was 1 (3.3%) subject with an event (relapsed) and 29 (96.7%) subjects who were censored (did not relapse as of data cut-off). Of the 29 subjects who were censored, 17 (58.6%) subjects were ongoing at data cut-off and 12 (41.4%) subjects discontinued early from the study without relapse.

It was not possible to estimate the median time to relapse for subjects in either treatment group because the censoring rate was very high and fewer than 50% of subjects relapsed.

Figure 7 Kaplan-Meier Curve for Time to relapse by Treatment Cohort (Safety Analysis Set)



IA = Interim analysis. IP = Investigational product.
Safety Analysis set includes all subjects who received any IP in Study 161505.
Curves are estimated using the Kaplan-Meier method. Time to relapse is calculated as: date of relapse – date of initial dose of IP in Study 161505 + 1. Subjects who did not relapse in Study 161505 are censored with time to censoring calculated as: date of treatment discontinuation or IA data cut-off – date of initial dose of IP in 161505 + 1.
Safety Analysis Set includes all subjects who received any IP in Study 161505.

- Change in R-ODS Score by ≥4 Points from Baseline

  A total of 77 out of 79 subjects had at least 1 postbaseline assessment of R-ODS, including 36 subjects in the Placebo – HyQvia treatment group and 41 subjects in the HyQvia – HyQvia treatment group. The mean (SD) baseline centile R-ODS score was 34.4 (9.50).

  At the time of data cut-off, 33 (42.9%) subjects overall had a decrease in raw R-ODS score by ≥4 points from baseline, of which 18 (50.0%) subjects were in the Placebo –HyQvia treatment group and 15 (36.6%) subjects were in the HyQvia –HyQvia treatment group.

- Change in Adjusted INCAT Disability Score from Baseline

  The mean baseline INCAT score was 2.3. Over the course of study, there were some small fluctuations in adjusted INCAT scores, but in general, adjusted INCAT scores remained below the baseline. At Week 96 and onwards, there were some slight increases in INCAT within the Placebo- HyQvia group (median =3.0). However, given the small sample size at such later time points, conclusions are limited. There were no differences observed based on dosing regimen.

- Change in Hand Grip Strength Score ≥8 kPa from Baseline

  A total of 78 out of 79 subjects had at least 1 postbaseline assessment of maximum hand grip strength, including 37 subjects in the Placebo –HyQvia treatment group and 41 subjects in the HyQvia –HyQvia treatment group.

  The overall proportion of subjects with a maximum hand grip strength change from baseline of ≥8 kPa decrease at the time of data cut-off was 42.31% (33/78 subjects), with similar percentages in the HyQvia –HyQvia treatment group as compared with the Placebo –HyQvia treatment group (43.90% [18/41 subjects] and 40.54% [15/37 subjects], respectively). No maximum hand grip strength change from baseline of ≥8 kPa was observed in any treatment group at any visit ≥ 24 months.

- Change in Medical Research Council Sum Scores from Baseline

  Mean baseline MRC sum score was 55.5 and similarly distributed between the treatment groups (Placebo - HyQvia = 55.1 and HyQvia - HyQvia = 55.9). Over the course of the study, the mean scores fluctuated

(range: 3.0 to -7.0) relative to mean baseline values with larger fluctuations appearing more often towards most distal timepoints where sample sizes were small. No differences were observed between treatment groups or dosing regimen.

Extrapolation to paediatric population

The pathophysiology of CIDP is similar in paediatric and adult population (Dziadkowiak et al. 2022). It is an immune-mediated disorder characterized by inflammatory changes and infiltration of macrophages and T-cells in the myelin sheath of the nerves. Chronic inflammation results in demyelination, remyelination, and onion bulb formation. Long-term demyelination leads to axonal loss. The amount of axonal loss determines the level of disability and long-term prognosis (Köller et al. 2005; Ulane and Brannagan 2012).

In accordance with the disease pathophysiology, treatment-response behaviour is similar in adults and paediatric CIDP patients; paediatric patients respond to immunoglobulin treatment, corticosteroids, and plasma exchange just like adult patients (McMillan et al. 2013). For these reasons, the latest CIDP guidelines do not differentiate between paediatric and adult CIDP populations for treatment recommendation (Van den Bergh et al. 2021).

A clinical study is highly impracticable in paediatric CIDP group. CIDP is a rare disease and recruitment of paediatric patients with CIDP into clinical studies is limited due to the low prevalence of disease in this age group. Although CIDP can occur at any age, its prevalence is particularly low in children, ranging approximately between 0.22-0.48 per 100,000 (Broers et al. 2019; Korinthenberg 1999; Łukawska et al. 2021; McMillan et al. 2013). Furthermore, the feasibility to conduct a paediatric clinical study is hampered by the low incentives of paediatric patients to enter a clinical study while effective treatments (such as IVIg) for CIDP are available. Lastly, recruitment of paediatric patients is complicated because of the reluctance of the parents or caregivers to expose children to the risks and discomfort of a clinical study. For all these reasons, it is anticipated that recruitment of paediatric patients in a prospective CIDP study is not feasible.

Although ADVANCE-1 did not include subjects <18 years old, there is experience with HyQvia in children with PID. Prior HyQvia studies included a total of 110 children between 2 and 17 years old (24 in Phase 3 study 160603, 15 in the Phase 3 extension study 160902 rolling over from 160603, 42 in EU Phase 4 study 161504 and 44 children in US Phase 3 study 161503) and a record of 10 years' clinical experience in adults and children. Accumulated data are consistent with a favourable safety profile in children. The formulation of HyQvia is the same for both diseases (including the rHuPH20 component) and the doses are similarly weight based. From a further safety standpoint, the gradual dose increases (Ramp up or Titration schedule) in both diseases with HyQvia helps ensure tolerability of the higher volumes required for CIDP.

Overall, given that the CIDP disease process and treatment response to IgG are similar in adults and paediatric patients, the MAH considers that safety and efficacy data of HyQvia from adults can be extrapolated to children/adolescents under 18.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

Study 161403 was a Phase 3, prospective, multicentre, double-blind, randomised, placebo-controlled study in adult patients with CIDP who had remained on a stable IVIg therapy. The study consisted of 2 parts: An SC treatment period (Epoch 1, HyQvia treatments or placebo) of up to 6 months and for subjects who relapsed during Epoch 1 an IV treatment period (Epoch 2, KIOVIG/Gammunex-C treatments) of 6 months. In general, the study followed the previous scientific advice recommendations, except for a suggested IVIg washout/withdrawal period prior to HyQvia treatment (see below). Of the 132 dosed subjects, 94 (excluding relapses and dropouts) completed Epoch 1. 10 subjects withdrew from Epoch for reasons other than relapse: AE-related discomfort, subjective worsening of symptoms not

meeting relapse shift criteria, and inability to travel for infusion visits. 21 subjects were enrolled in Epoch 2 and 7 subjects who relapsed decided not to rollover to Epoch 2. Only Epoch 1 will be discussed since Epoch 2 does not include HyQvia treatments. Demographic and baseline characteristics were generally balanced between the two treatment arms. The study population was adequately selected. Only patients with confirmed CIDP diagnosis and on stable IVIg treatment were eligible.

Efficacy data and additional analyses

Study 161403 met the primary endpoint and demonstrated that maintenance treatment with HyQvia significantly reduced the CIDP relapse rate when compared to placebo. Relapse was defined as an increase of $\geqslant$1 point relative to the pre-SC treatment baseline score in 2 consecutive adjusted INCAT disability scores. The second INCAT assessment to confirm the diagnosis of relapse was in contrast to previous CIDP trials (Hughes et al., 2018, Hughes et al., 2008, van Schaik et al., 2018), which used a single INCAT-based relapse definition. The INCAT score is often used as primary endpoint in CIDP studies, however, this stricter definition of relapse may have contributed to the lower numbers of relapses in study 161403. For the primary efficacy endpoint, a significant difference in CIDP relapse was demonstrated in favor of HyQvia (9,7% vs 31.4%, p=0.0045). Given the additional burden of CIDP relapse on functional capacity and disease progression, this level of relapse reduction could be considered clinically relevant. However, missing values not explained in detail and intercurrent events with unknown (or undefined) influence on the development of a relapse occurred and gave rise to some uncertainties regarding the magnitude and interpretation of the primary (and important secondary) endpoints. In detail, 8 patients with missing relapse determination (2 and 6 patients in the Placebo and HyQvia arm) were imputed as "no relapse". Furthermore, 10 patients discontinued early prior to relapse (of which 3 had missing relapse determination). The MAH was asked to provide further details on the imputations of these missing values and provided revised primary analyses and sensitivity analyses (including a tipping point analysis and a worst-case scenario on the ITT population). Furthermore, defined definitions of a suitable estimand and according analyses were requested. For some patients, the reason for early discontinuation appeared to be due to CIDP worsening. Therefore, simply imputing these patients as "no relapse" is considered anti-conservative and results in biased estimates. In the revised primary analysis provided, the MAH has defined the ICEs with corresponding strategies such that for example treatment discontinuation due to CIDP worsening would be addressed with a composite strategy and thus these patients were considered as "relapse" in the analysis. Missing values were also imputed depending on the reason for missingness. The revised primary analysis resulted in a relapse rate of 31.7% (95% CI: 21.96, 43.39) vs. 15.5% (95% CI: 8.36, 26.84) for the Placebo and HyQvia arm (treatment difference -16.2% (95% CI: -29.92; -1.27%)). Results provided in the sensitivity analyses showed consistent results with the revised primary analysis. Given the nature of the reasons for missings or early discontinuation, the revised primary analysis provide a more reasonable estimate for the relapse rates than the original primary analysis. The MAH updated the section 5.1 of the SmPC with the revised estimates and provided more information on "relapse" imputation in the 100 000 simulations.

Moreover, the observed relapse rate for HyQvia in the primary analysis is within the range of 6-month relapse rates published for other IG products in CIDP patients with stable disease (5% to 13%, Hughes et al., 2008, van Schaik et al., 2018). Subgroup analysis (sex, age, race, dosing regimen, geographic region) revealed no clinically relevant differences for the primary endpoint. Of note, the numbers in some subgroups were too small to draw meaningful conclusions. Additional subgroup analyses were provided for the secondary endpoints evaluating for age, sex and geographic region. Some discrepancies were noted between regions, which were discussed by the MAH and most likely due to differences in the baseline characteristics. This was considered acceptable by the CHMP.

Unlike other studies (e.g. the Study IgPro20_3003, ICE study or study IgPro10_3001), there was no washout of the previous IVIg treatment or no IVIg withdrawal period prior to treatment with HyQvia in Epoch 1. Hence, it is not known how many patients were enrolled who still needed IgG treatments/ were

in remission at the time of the study 161503 and whether these patients were equally randomized to the cohorts. It is recommended that IVIG doses in CIDP are tapered periodically to assess the ongoing need for continued therapy. If symptoms return after IG withdrawal, treatment is reinstated (GL: van den Bergh et al., 2021). For example, in the RMC trial, 44% of CIDP patients were able to reduce their IVIG or corticosteroid dose but still responded, indicating that they were receiving a higher dose than necessary (RMC Trial Group, Lancet Neurol., 2009).

Compared to SCIg (33%/39% for SCIG doses and 63% for placebo), relapse rates were considerably lower in both the verum and placebo group (15.5% HyQvia and 31.7% placebo) (van Schaik et al., 2018). This may indicate that subjects in remission were included in the present study. Importantly, in the placebo group of the study 161403 Epoch 1, 68.6% of subjects showed no deterioration within 24 weeks, which was a higher number than previously observed in the PATH study (van Schaik et al, 2018; 37% on placebo did not relapse). As only IVIg-dependent CIDP patients were enrolled, it is very unlikely that the placebo effect observed in the PATH study was due to disease variability. Possible reasons for this placebo effect were found to be older age, more severe disease, and a longer time to deterioration in the IgG-dependency test period. In the present study, 38.2% of subjects > 55 years and 25% of subjects ≤55 years on placebo relapsed, indicating a similar trend. The importance of placebo effects/responses was further supported by a meta-analysis of 13 studies showing that 57% of subjects randomized to placebo experienced worsening while 43% did not relapse (Lewis et al., 2020). In addition, a carry-over effect from previous IVIG treatment may have confounded efficacy assessments for up to 10 weeks, almost half the duration of the pivotal trial. Therefore, the primary analysis may have overestimated the treatment effect of HyQvia in preventing relapses compared to placebo. However, it has to be noted that according to the SmPC, patients in the real-world practice will also be treated with HyQvia 2 weeks after their last IVIg treatment.

All three secondary efficacy endpoints supported the primary analysis. Fewer subjects in the HyQvia group (37.5%) experienced worsening of functional disability compared to the placebo group (54.4%). More specifically, in the HyQvia group worsening defined by RODS (23.2%) was experienced by more subjects than worsening defined by hand grip strength (14.3%) or INCAT sensory score (10.7%). Of note, the number of subjects experiencing worsening defined by RODS was almost comparable between verum (23.2%) and placebo (29.4%). Disease worsening experienced even during HyQvia treatments may be attributed to normal disease fluctuations and variability, and it was discussed whether required doses of HyQvia need to be higher than of pre-study IVIG (in line with slightly lower serum trough IgG levels observed in the PK substudy). The differences in the summary of worsening of functional disability were marginally non-significant between treatment arms (p=0.0896), but still can be considered clinically meaningful. Possible reasons for the lack of statistical significance were discussed by the MAH to be a loss of power to reach the 0.05 threshold due to the dichotomous nature of this endpoint. Additionally, an early separation of the Kaplan-Meier curves was observed around week 4, with a significant difference in time to relapse between HyQvia and placebo (Wilcoxon survival test, p=0.002). Due to high censoring rates in both groups, median time to relapse could not be estimated. Mean RODS centile metric scores showed significant differences between HyQvia treatments and placebo treatments, with worsening experienced in subjects on placebo. The MAH assessed the relationship between serum trough IgG levels and clinical outcome, but was not conclusive (which is in line with literature). In addition, the MAH addressed missing data from some subjects for the R-ODS or the composite endpoint of functional worsening and discussed the clinical relevance of the composite endpoint of functional worsening.

Moreover, tertiary efficacy analyses supported the results of the primary analysis by demonstrating more favourable changes in INCAT, MRC, grip strength, and R-ODS subscores in the HyQvia group compared to the placebo. While the scores in most domains of the Health-related quality of life assessments remained relatively constant or improved in the HyQvia group, scores in the placebo group showed a trend towards deterioration. As HyQvia allows larger volumes to be infused subcutaneously in a relatively short time (125.9 minutes), patient satisfaction and preference are important outcomes to consider and are reflected in the analyses of patient-reported outcomes. Indeed, median global satisfaction and median

effectiveness scores were higher in the HyQvia group than in the placebo group. Evaluation of treatment preference among those completing Epoch 1, which compared pre-study treatment (IVIg) with HyQvia demonstrated that approximately two-thirds of subjects preferred HyQvia over their pre-study IVIg, and most subjects preferred the study drug in terms of "scheduling their treatment" and "convenience" with 59% and 67.6%, respectively. Among the HyQvia group, 83.3% indicated they would choose to continue HyQvia over their pre-study drug at the end of the study.

Nevertheless, efficacy assessments in Epoch 1 were limited to 6 months. Long-term efficacy information is being collected in the ongoing open-label long-term extension study 161505 in which all subjects who completed Epoch 1 (from both the placebo and HyQvia arm) are offered an open-label treatment with HyQvia. Interim results indicate that a higher number of subjects on HyQvia who had already received HyQvia in Epoch 1 (4 of the 5 who relapsed) relapsed compared to subjects on former placebo (1 of the 5 who relapsed). Moreover, 42.9% of subjects exhibit a ≥ 4 point decrease in raw R-ODS score from baseline. Changes in R-ODS score are not consistent with clinical worsening defined by an increase in the adjusted INCAT score, suggesting that most R-ODS changes reflect clinically insignificant fluctuations in CIDP symptoms. Overall, the efficacy results from this study should be interpreted in the context of the long follow-up period (169 patient-years). Uncertainty still exists on the long-term efficacy of HyQvia as a maintenance treatment in CIDP, as only interim results of the extension study 161505 are currently available. The MAH confirmed that they will submit the final study results in April 2024.

By pooling the final results of study 161403 and the interim results of 161505, a relapse rate of 10% was observed with a 6-month relapse rate of 2.6%. However, 16 missing relapse determinations may have confounded the analysis. When imputed as relapse, the 6-month relapse rate was estimated to be 7.4% which is still within the range of reported 6-months rates (Hughes et al., 2008, van Schaik et al., 2019).

In conclusion, the results of the studies included in this variation provide evidence for HyQvia as maintenance treatment in CIDP. The efficacy of HyQvia in preventing relapses is comparable to other approved IG treatments in CIDP. Without applying a conversion factor, the dosing regimen for HyQvia was equivalent to the subject's pre-randomization monthly IVIg dose (mean dose 1.1 g/kg per month). This was at the lower end of the guideline-recommended dose range for maintenance treatment in CIDP (Allen et al., 2020) and within the range of the maintenance doses of conventional SCIg in CIDP (0.2 or 0.4 g/kg/wk). The 1:1 conversion factor for transitioning from IVIg to SCIg has also been used before (Hadden et al., 2018, Cocito et al., 2016, Markvardsen et al, 2016). However, higher doses of HyQvia may be needed to prevent relapses in the long term, as serum trough IgG levels were also slightly lower compared to baseline/pre-study IVIg therapy. A statement regarding dose reductions or adaptations according to the individual clinical response was added to the SmPC. Overall, the positive results of these studies justify a transition from IVIg treatment to SCIg treatment in CIDP maintenance therapy. The posology range given in the PI for patients previously treated with IVIg is supported.

Most importantly, HyQvia is only allowed to be indicated as maintenance therapy in patients previously stabilized on IVIg in line with the clinical trial design. The MAH has appropriately updated the wording of the indication as requested by the CHMP. Information regarding dosing guidance for CIDP patients naïve to IGs were removed as requested, as induction therapy with HyQvia is not supported by clinical data or by currently available literature data (Markvardsen et al. 2017; Allen et al., 2020, Goyal et al., 2021). The dosing recommendations for patients previously treated with conventional SCIg were found to be insufficiently justified and removed from the SmPC as well. Reasons include the lack of clinical data in CIDP patients switching from conventional SCIg to HyQvia, inconsistency with the wording of the indication and other approved SCIg products in this indication. Specific head-to-head trials comparing the efficacy of IVIg and SCIg as induction therapy are currently lacking.

Assessment of paediatric extrapolation

The MAH argued that the pathophysiology of CIDP is similar in the paediatric and adult population. Due to the low prevalence of CIDP in children/adolescents, the conduct of clinical trials in this age group is highly

impractical (e.g. low recruitment, missing consent from parents for their children to participate in a trial, and available effective treatment opinions). Furthermore, the safety profile of HyQvia in paediatric PID patients has been favourable. Doses are based on body weight and are gradually increased according to the recommended titration schedule. Overall, extrapolation to the paediatric population is justified and the paediatric indication was adequately added in the SmPC.

2.4.3. Conclusions on the clinical efficacy

HyQvia was more effective than placebo in preventing relapse of neuromuscular disability, irrespective of age, sex, dosing regimen and geographic location, and was supported by prespecified sensitivity analysis. A revised primary analysis in which missing data were imputated depending on the reason for missingness provided a more reasonable estimate for the relapse rates than the original primary analysis. The SmPC was updated accordingly with the revised estimates. Results of the secondary and tertiary efficacy endpoints were consistent with the analyses of relapse rates and indicated that HyQvia was more effective than placebo in preventing functional deterioration in CIDP. The change in INCAT and other functional scores (MRC, grip strength) from baseline to Epoch 1 completion was in the expected direction and supported HyQvia over placebo. Mobility and self-care were improved for the HyQvia group compared to placebo. Overall treatment satisfaction was better in the HyQvia group than the placebo group. Two-thirds of subjects in the HyQvia arm preferred HyQvia over their pre-study IVIg. Overall, across all of these PRO assessments, the results were in favor of HyQvia.

Interim results of the study 161505 were provided in this variation evaluating the long-term safety and efficacy of HyQvia in adult CIDP patients. The interim analysis mainly supports the primary efficacy analysis of the pivotal study 161403 in preventing relapse of neuromuscular disability and impairment in CIDP patients, and final results will be submitted by April 2024.

The CHMP concluded that the efficacy data available support the following indication:

Immunomodulatory therapy in adults, children and adolescents (0 to 18 years) in:

• Chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilization with IVIg.

2.5. Clinical safety

Introduction

The safety analysis set consists of all subjects who received at least one dose of HyQvia in Study TAK-771-1001, Study 161403, and Study 161505. The HyQvia CIDP analysis set consists of subjects with CIDP who were exposed to HyQvia in Study 161403 Epoch 1 or Study 161505. Data from Study 161403 Epoch 2 were excluded since the subjects received open-label IVIg as rescue treatment for relapse.

Patient exposure

A total of 151 subjects were exposed to HyQvia in Study TAK-771-1001, Study 161403 Epoch 1, and Study 161505. A pooled analysis of safety data from the participants who received HyQvia in the 2 CIDP studies (Study 161403 Epoch 1 and Study 161505) has been conducted. This analysis included 100 subjects. Overall, subjects received a mean of 23.4 months of treatment with HyQvia, 3188 infusions, and a mean of 31.9 infusions per subject. The average time to deliver the dose was 125.9 minutes. This pooled analysis was the longest follow-up study performed within the context of a CIDP clinical trial; total follow-up time was 194.6 patient-years.

In Study 161403 Epoch 1, the mean duration of exposure to study treatment was 5.3 months in the HyQvia group and 4.7 months in the placebo group. The duration of exposure was ≥6 months for 69.4% and 58.6% of subjects in the HyQvia and placebo groups, respectively. In the HyQvia group, a total of

600 study drug and 600 rHuPH20 infusions were administered. In the placebo group, a total of 646 study drug infusions and 645 rHuPH20 infusions were administered.

As of the cut-off date for the interim analysis (23 Feb 2022), a total of 79 subjects had received at least 1 dose of HyQvia during Study 161505. The mean duration of exposure to HyQvia was 24.9 months and generally similar in both treatment groups. Approximately half of the subjects had an exposure to HyQvia of ≥24 months. A total of 2595 HyQvia infusions were administered. Among these 2595 infusions, one infusion (0.0389%), which was the last infusion in Study 161403 prior to enrolling in Study 161505, was incorrectly recorded as an infusion in Study 161505.

72/1247 (5.8%) of infusions were interrupted/ stopped or rate reduced in 161403 Epoch 1. Among the 2595 infusions until the DLP in study 161505, 103 (4.0%) infusions were interrupted/stopped or had the infusion rate reduced.

Study 161403

Overall, 89 subjects (67.4%) reported 491 TEAEs. Among these 491 TEAEs, 276 were related to the IP, 8 were severe TEAEs, 4 were severe TEAEs related to IP, 7 were serious TEAEs, and 6 were serious TEAEs related to IP. Of note, one subject in the placebo group experienced 2 severe TEAEs. Four subjects (3.0%) reported 6 TEAEs that led to early discontinuation from Epoch 1. No TEAE resulted in death.

There were 0.39 TEAEs per infusion, 3.72 TEAEs per subject, and 8945.42 TEAEs per 1000 subject-years. The number of TEAEs per subject was 5.52 in the HyQvia group compared to 2.13 in the placebo group.

In the HyQvia group, 38 subjects (61.3%) reported a total of 223 TEAEs related to IP compared to 19 subjects (27.1%) who reported 53 TEAEs in the placebo group. A lower percentage of subjects in the HyQvia group compared to the placebo group had any severe TEAE, any severe TEAE related to IP, any serious TEAE, and any serious TEAE related to IP. The number of TEAEs per infusion, per subject, and per 1000 subject-years were higher in the HyQvia group than in the placebo group.

Table 26 Treatment-Emergent Adverse Events in Epoch 1 by Treatment Group, Overall Summary (Epoch 1 Safety Analysis Set)

	Placebo (N = 70)		HYQVIA (N = 62)		Total (N = 132)	
Category	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events	Number (%) of Subjects	Number of Events
Any TEAE	40 (57.1)	149	49 (79.0)	342	89 (67.4)	491
Any TEAE related to IP	19 (27.1)	53	38 (61.3)	223	57 (43.2)	276
Any severe TEAE	6 (8.6)	7	1 (1.6)	1	7 (5.3)	8
Any severe TEAE related to IP	3 (4.3)	3	1 (1.6)	1	4 (3.0)	4
Any serious TEAE	5 (7.1)	5	2 (3.2)	2	7 (5.3)	7
Any serious TEAE related to IP	5 (7.1)	5	1 (1.6)	1	6 (4.5)	6
Any TEAE leading to early discontinuation from Epoch 1	1 (1.4)	1	3 (4.8)	5	4 (3.0)	6
Any TEAE with outcome of death	0	0	0	0	0	0

Adverse events

Table 27 is an overview of TEAEs that occurred as the combined total in all studies (Study TAK 771-1001, Study 161403 Epoch 1, and Study 161505) and the combined total in HyQvia CIDP studies (Study 161403 Epoch 1 and Study 161505).

89 subjects (89.0%) from Study 161403 Epoch 1 and Study 161505 reported 1515 TEAEs. Among these 1515 TEAEs (41 of which were severe), 887 were related to HyQvia (20 of which were severe), and 20

were serious TEAEs (3 of which were related to HyQvia). There were 0.48 TEAEs per infusion and 15.2 TEAEs per subject.

Table 27 Overview of Adverse Events That Occurred During or After HyQvia Infusion (Studies 161403, 161505, 771-1001: All Safety Subjects)

Category	HyQvia[a] (N[b]=151)		HyQvia CIDP[a] (N[b]=100)	
	Number (%) of Subjects[c]	Number of AEs and rate per 100 infusions[d]	Number (%) of Subjects[c]	Number of AEs and rate per 100 infusions[d]
Any TEAE	140 (92.7)	1937 (57.6)	89 (89.0)	1515 (47.5)
Any TEAE related to IP	70 (46.4)	887 (26.4)	70 (70.0)	887 (27.8)
Any severe TEAE	16 (10.6)	41 (1.2)	16 (16.0)	41 (1.3)
Any severe TEAE related to IP	7 (4.6)	20 (0.6)	7 (7.0)	20 (0.6)
Any serious TEAE	16 (10.6)	20 (0.6)	16 (16.0)	20 (0.6)
Any serious TEAE related to IP	3 (2.0)	3 (0.1)	3 (3.0)	3 (0.1)
Any TEAE leading to early discontinuation from Epoch 1	7 (4.6)	9 (0.3)	7 (7.0)	9 (0.3)
Any TEAE with outcome of death	1 (0.7)	1 (0.0)	1 (1.0)	1 (0.0)

AE=adverse event; CIDP=chronic inflammatory demyelinating polyradiculopathy; IP=investigational product; TEAE=treatment-emergent adverse event
a HyQvia: Studies 161403 (Epoch 1 subjects who received HyQvia), 161505 and TAK-771-1001. HyQvia CIDP: Studies 161403 (Epoch 1 subjects who received HyQvia) and 161505.
b Number of subjects in the Safety Analysis set.
c Rate by subject = Total number of subjects experiencing the AE divided by the total number of subjects in the respective treatment group (N) and multiplied by 100.
d Rate per 100 infusions = Total number of AEs divided by the total number of infusions in the respective treatment group (N) and multiplied by 100.
For the columns of 'Number (%) of subjects': Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.

Systemic and Local Adverse Events Associated with HyQvia Infusions

Common systemic and local adverse events included injection site erythema, headache, erythema, pyrexia, infusion site oedema and infusion site erythema. These TEAEs are consistent with the published rates with other IgG products as well as with the known safety profile of HyQvia. No new safety signal was detected. Some common temporally-associated systemic TEAEs reported with IV administration of IgG such as hemodynamic changes, nausea/vomiting, and flu-like symptoms (Table 28) were less commonly observed in these studies.

Table 28 Common Systemic and Local Adverse Events in Study 161403 Epoch 1 and Study 161505

System Organ Class Preferred Term	Systemic AEs Rate per 100 Infusions	Local AEs Rate per 100 Infusions
General Disorders and Administration Site Conditions		
Infusion Site Erythema		6.932
Infusion Site Oedema		2.039
Injection Site Erythema		1.255
Pyrexia	2.290	
Nervous System Disorders		
Headache	4.360	
Skin and Subcutaneous Tissue Disorders		
Erythema		2.509

Table 29. Temporally Associated or Casually Related Adverse Events That Occurred During or After HyQvia Infusion, by Preferred Term Categorization (Studies 161403, 161505: Safety Analysis Set)

HyQvia CIDP[a]: N[b] = 100 subjects; N[c] = 3188 infusions

Preferred Term Grouping[d]	Number and Rate by Subject n (%)[e]	Number of AEs and Rate per 100 Infusions n (%)[f]
Flu-like Illness	30 (30.0)	95 (3.0)
Nausea/Vomiting	14 (14.0)	18 (0.6)
Hemodynamic Changes	5 (5.0)	14 (0.4)

In addition, the MAH provided pooled results of the ADRs including data from 4 clinical trials in 124 PID patients receiving 3202 infusions (160602, 160603, 160902, and 161101) and from 2 clinical studies in 100 CIDP patients receiving 3188 infusions (161403 and 161505).

Table 30 Adverse drug reactions reported in HyQvia studies 160602, 160603, 160902, 161101, 161403 and 161505

System Organ Class	Adverse Drug Reaction	Number and Rate (%) by Subject[b] (N = 224) n (%)	Category	Number and Rate (%) by Infusions[c] (M = 6390) m (%)	Category
Nervous system disorders	Headache	82 (36.6)	Very Common	277 (4.33)	Common
	Dizziness	21 (9.4)	Common	35 (0.55)	Uncommon
	Migraine	12 (5.4)	Common	25 (0.39)	Uncommon
	Tremor	6 (2.7)	Common	7 (0.11)	Uncommon
	Paraesthesia	5 (2.2)	Common	7 (0.11)	Uncommon
Nervous system disorders	Cerebrovascular accident and Ischaemic stroke	2 (0.9)	Uncommon	2 (0.03)	Rare
Cardiac disorders	Sinus tachycardia and Tachycardia	12 (5.4)	Common	17 (0.27)	Uncommon
Vascular disorders	Blood pressure increased and Hypertension	23 (10.3)	Very Common	36 (0.56)	Uncommon
	Hypotension	3 (1.3)	Common	5 (0.08)	Rare
Respiratory, thoracic and mediastinal disorders	Dyspnoea	6 (2.7)	Common	6 (0.09)	Rare
Gastrointestinal disorders	Nausea	48 (21.4)	Very Common	108 (1.69)	Common
	Abdominal pain, Abdominal pain lower, Abdominal pain upper and Abdominal tenderness	38 (17.0)	Very Common	68 (1.06)	Common
	Diarrhea	36 (16.1)	Very Common	52 (0.81)	Uncommon
	Vomiting	33 (14.7)	Very Common	51 (0.80)	Uncommon
	Abdominal distension	6 (2.7)	Common	14 (0.22)	Uncommon
Skin and subcutaneous tissue disorders	Erythema	15 (6.7)	Common	88 (1.38)	Common
	Pruritus	15 (6.7)	Common	27 (0.42)	Uncommon
	Rash, Rash erythematous, Rash macular, Rash maculo-papular and Rash papular	16 (7.1)	Common	25 (0.39)	Uncommon
	Urticaria	8 (3.6)	Common	8 (0.13)	Uncommon

Musculoskeletal and connective tissue disorders	Myalgia	21 (9.4)	Common	62 (0.97)	Uncommon
	Arthralgia	32 (14.3)	Very Common	60 (0.94)	Uncommon
	Limb discomfort and Pain in extremity	19 (8.5)	Common	45 (0.70)	Uncommon
	Back pain	21 (9.4)	Common	28 (0.44)	Uncommon
Musculoskeletal and connective tissue disorders	Joint stiffness	1 (0.4)	Uncommon	12 (0.19)	Uncommon
	Musculoskeletal chest pain	7 (3.1)	Common	11 (0.17)	Uncommon
	Groin pain	3 (1.3)	Common	4 (0.06)	Rare
Renal and urinary disorders	Hemosiderinuria	3 (1.3)	Common	3 (0.05)	Rare
General disorders and administration site conditions	Local reactions (Total)	132 (58.9)	Very Common	1193 (18.67)	Very Common
General disorders and administration site conditions	•Infusion site discomfort, Infusion site pain, Injection site pain, Puncture site pain and Tenderness	91 (40.6)	Very Common	422 (6.60)	Common
	•Infusion site erythema and Injection site erythema	59 (26.3)	Very Common	384 (6.01)	Common
	•Infusion site oedema, Injection site oedema, Infusion site swelling, Injection site swelling and Swelling (local)	45 (20.1)	Very Common	175 (2.74)	Common
	•Infusion site pruritus, Injection site pruritus, Puncture site pruritus and Vulvovaginal pruritus	32 (14.3)	Very Common	100 (1.56)	Common
General disorders and administration site conditions	•Infusion related reaction	6 (2.7)	Common	20 (0.31)	Uncommon
	•Infusion site bruising, Injection site bruising, Infusion site haematoma, Injection site haematoma, Infusion site haemorrhage and Vessel puncture site bruise	12 (5.4)	Common	19 (0.30)	Uncommon
	•Infusion site reaction, Injection site reaction and Puncture site reaction	9 (4.0)	Common	13 (0.20)	Uncommon
General disorders and administration site conditions	•Infusion site mass, Injection site mass and Infusion site nodule	7 (3.1)	Common	12 (0.19)	Uncommon
	•Infusion site discolouration	5 (2.2)	Common	12 (0.19)	Uncommon
	•Infusion site rash and Injection site rash	4 (1.8)	Common	11 (0.17)	Uncommon
	•Infusion site induration and Injection site induration	5 (2.2)	Common	10 (0.16)	Uncommon
General disorders and administration site conditions	•Infusion site warmth	5 (2.2)	Common	6 (0.09)	Rare
	•Infusion site paraesthesia and Injection site paraesthesia	3 (1.3)	Common	6 (0.09)	Rare
	•Infusion site inflammation	3 (1.3)	Common	3 (0.05)	Rare
	Feeling hot and Pyrexia	48 (21.4)	Very Common	126 (1.97)	Common
General disorders and administration site conditions	Asthenia, Fatigue, Lethargy and Malaise	55 (24.6)	Very Common	124 (1.94)	Common
	Chills	7 (3.1)	Common	24 (0.38)	Uncommon
	Oedema, Oedema peripheral and Swelling (systemic)	13 (5.8)	Common	23 (0.36)	Uncommon
	Localised oedema, Peripheral swelling and Skin oedema	7 (3.1)	Common	10 (0.16)	Uncommon

General disorders and administration site conditions	Gravitational oedema, Oedema genital, Scrotal swelling and Vulvovaginal swelling	5 (2.2)	Common	8 (0.13)	Uncommon
	Burning sensation	2 (0.9)	Uncommon	7 (0.11)	Uncommon
	Hyperhidrosis	3 (1.3)	Common	5 (0.08)	Rare
Investigations	Coombs direct test positive and Coombs test positive	4 (1.8)	Common	4 (0.06)	Rare

Adverse Drug Reactions (ADRs) are selected based on the assessment by the sponsor. All ADRs that occurred during or after first dose are presented in the table, regardless of the relationship assessed by the investigator. For analysis purposes certain preferred terms were collapsed.
N = Total number of subjects in the Safety Analysis Set. M = Total number of infusions. n = Number of subjects with an ADR within the respective preferred term. m = Number of adverse events within the respective preferred term.
ADR frequency is based upon the following scale: Very Common (>=1/10), Common (>=1/100 - <1/10), Uncommon (>=1/1,000 - <1/100), Rare (>=1/10,000 - <1/1,000), Very Rare (<1/10,000).
[a]based on data of the interim CSR.
[b]Rate by subject = total number of subjects experiencing the ADR (n) divided by total number of subjects (N) multiplied by 100.
[c]Rate by infusions = total number of ADRs (m) divided by total number of infusions (M) multiplied by 100.
MedDRA version of the source data: 24.1.

Serious adverse event/deaths/other significant events

- *Serious Adverse Events (SAE)*

Overall, there were 20 SAEs that occurred during or after HyQvia infusion. There were no SAEs that occurred during or after HyQvia infusion in >5% of subjects or in >1 per 100 infusions. Only 1 of the 20 SAEs was assessed as related to HyQvia infusion and was severe. The subject, a 48-year-old female, suffered a cerebrovascular accident (acute stroke) 2 days after the last HyQvia dose on day 17, (interval 4 weeks, 0.4g/kg BW). The subject was discontinued from the study. Neuroimaging studies revealed middle cerebral artery occlusion developed at the setting of an atherosclerotic plaque in the ipsilateral carotid artery. This subject had chronic hypertension as a risk factor for atherosclerosis.

- *Adverse events of special interest (AESIs)*

The definition of AESIs included allergic reactions, local and systemic immune complex mediated reactions, and thrombotic and embolic events. A total of 8 subjects experienced AESIs during or after treatment with HyQvia in Study 161403 and Study 161505.

Table 31. Adverse Events of Special Interest That Occurred During or After HyQvia Infusion by MedDRA System Organ Class (Studies 161403, 161505: Safety Analysis Set)

HyQvia CIDP[a]: N[b] =100 subjects; N[c] =3188 infusions

System Organ Class	Preferred Term	Number and Rate by Subject n (%)[f]	By Subject Frequency Category[d]	Number of AEs and Rate per 100 Infusions n (rate)[g]	By Infusion Frequency Category[e]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	INFUSION SITE INDURATION	2 (2.00)	Common	5 (0.157)	Uncommon
	INFUSION SITE NODULE	1 (1.00)	Common	4 (0.125)	Uncommon
	INFUSION SITE PAIN	1 (1.00)	Common	4 (0.125)	Uncommon
NERVOUS SYSTEM DISORDERS	CEREBROVASCULAR ACCIDENT	1 (1.00)	Common	1 (0.031)	Rare
	ISCHAEMIC STROKE	1 (1.00)	Common	1 (0.031)	Rare
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ANGIOEDEMA	1 (1.00)	Common	1 (0.031)	Rare
VASCULAR DISORDERS	THROMBOPHLEBITIS SUPERFICIAL	1 (1.00)	Common	1 (0.031)	Rare

AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities
[a] HyQvia CIDP: Studies 161403 (Epoch 1 subjects who received HyQvia) and 161505.
[b] Number of subjects in the Safety Analysis Set.
[c] Total number of infusions.
[d] Frequency has been evaluated using the following criteria: very common (≥10.00%), common (9.99-1.00%), uncommon (0.99-0.10%), rare (0.09%-0.01%), and very rare (<0.01%), eg, an event (preferred term) is defined as "very common" if it occurs in more than or equal to 10% of subjects.
[e] Infusion frequency has been evaluated using the following criteria: very common (≥10 per 100 infusions), common (9.99-1 per 100 infusions), uncommon (0.99-0.10 per 100 infusions), rare (0.09-0.01 per 100 infusions), and very rare (<0.01 per 100 infusions), eg, an event (preferred term) is defined as "very common" if it occurs in more than or equal to 10 per 100 infusions.
[f] Rate by subject = Total number of subjects experiencing the AE divided by the total number of subjects in the respective study/treatment group (N) and multiplied by 100.
[g] Rate per 100 infusions = Total number of AEs divided by the total number of infusions in the respective study/treatment group (N) and multiplied by 100.
Adverse events of special interest include allergic reactions, local immune complex mediated reactions, systemic immune complex mediated reactions, and thrombotic and embolic events.

- *Deaths*

There were no deaths reported in Study TAK-771-1001 or Study 161403. One death was reported in Study 161505; 1 subject died at Study Day 41 due to cholangiocarcinoma. This death was assessed as unrelated to study treatment.

Laboratory findings

Assessment of haemolysis and other clinical laboratory parameters did not raise any safety concerns over the course of the study. In the study 161505, the toxicity grade for serum total bilirubin, sodium, and potassium worsened from Grade <3 at baseline to Grade 3 or higher in 1 to 2 subjects and for lymphocytes in 13 subjects at multiple timepoints.

Safety in special populations

In the HyQvia CIDP analysis set (N=100), the mean age was 54.0 years, and included equal proportions of subjects ≤55 years of age (50.0%) and >55 years of age (50.0%). More male subjects (57.0%) were enrolled compared to female subjects (43.0%). In Study TAK-771-1001, more female subjects (56.9%) were enrolled compared to male subjects (43.1%), and all subjects were ≤55 years of age.

Overall, subjects ≤55 years of age experienced more TEAEs (50.8%) than subjects >55 years old (44.6%). However, AR/SAR rates were similar between subjects ≤55 years of age (32.9%) and subjects >55 years of age (31.4%).

More female subjects experienced TEAEs (53.7%) compared to male subjects (42.3%). Adverse reaction/suspected adverse reaction rates per 100 infusions were similar between male subjects (30.8) and female subjects (33.8).

Immunogenicity

A total of 15 subjects receiving HyQvia developed binding antibodies (≥1:160) to rHuPH20; 1 of these subjects also had neutralizing antibodies. The presence of binding or neutralizing anti rHuPH20 antibodies was not associated with an increased rate of TEAEs. There were 7 subjects who developed positive binding antibodies in Study 161403 and 14 subjects in Study 161505. There were 6 subjects who had positive binding antibodies in both Study 161403 and Study 161505.

Two subjects who received placebo in Study 161403 Epoch 1 developed binding antibodies in Study 161505. More frequent detection of binding antibodies in subjects who were exposed to HyQvia could be due to passive transfer of antibodies that can exist in the pool of plasma from which the IGI component of HyQvia was prepared (Rosengren et al., 2015). Treatment-emergent adverse event rates were similar

in subjects with negative antibody titers (47.7 per 100 infusions) compared to subjects with positive antibody titers (47.0 per 100 infusions). Adverse reaction/suspected adverse reaction rates were similar in subjects with negative antibody titers (34.3 per 100 infusions) compared to subjects with positive antibody titers (26.2 per 100 infusions).

One subject receiving placebo and rHuPH20 only developed binding antibodies to rHuPH20.

Discontinuation due to adverse events

7 patients of the HyQvia CIDP group (7%) experienced a total of 9 TEAEs that led to the early discontinuation from HyQvia. The 6 possibly related AEs that led to discontinuation of 4 subjects from the studies were acute stroke, infusion site oedema and infusion site pain, nausea and chills, and hand weakness increased from baseline CIDP. 3 unrelated AEs included abdominal cramp, cholangiocarcinoma and mantle cell lymphoma experienced each by 1 subject. Only the case of cholangiocarcinoma was fatal, all other subjects recovered/were recovering.

Study TAK-771-1001

All 51 subjects in Study TAK-771-1001 experienced 422 TEAEs; 402 local and 20 systemic TEAEs. All TEAEs were mild in severity, and all recovered/resolved by the end of the study. No severe TEAEs were reported during the study. One subject in the low TDL Ramp-Up dosing group had an elective abortion that was classified as an SAE, which was considered not related to the study drug by the investigator. No TEAEs leading to study discontinuation were reported during the study.

The most reported TEAEs (occurring in >50% of subjects) were infusion site swelling, infusion site erythema, infusion site pain, and infusion site pruritus. Systemic TEAE rates were 15.2% in the Ramp-Up group (n=33) and 38.9% in the No Ramp-Up group (n=18). The high TDL/No Ramp-Up dosing group had the highest incidence of systemic AEs (5 [50.0%] subjects experienced 11 TEAEs).

The number of subjects who discontinued the study was 12.1% in Ramp-Up and 50% in No Ramp-Up groups. Discontinuation rate was higher in the high TDL/No Ramp-Up dosing group (70.0%) compared to all other treatment arms (range, 22.2%-25.0%). The rate of TEAEs per infusion was higher in the No Ramp-Up dosing group (3.03) compared to the Ramp-Up dosing group (2.26). The rate of TEAEs per subject was higher in the Ramp-Up dosing group (9.30) compared to the No Ramp-Up dosing group (6.39). However, the rate of TEAEs per subject-year was comparable between the Ramp-Up dosing group (65.81) and the No Ramp-Up dosing group (66.36). Accelerated ramp-up revealed similar TEAE and discontinuation rates compared to the conventional (slower) ramp-up.

Overall, HyQvia with and without Ramp-Up dosing was safe and well tolerated in healthy subjects. Higher subject dropout rate in the high TDL-No Ramp-Up dosing group compared to all other treatment groups suggests that tolerability could be improved with Ramp-Up dosing, especially when high doses of HyQvia need to be administered. The findings from Study TAK-771-1001 indicate that ramp-up tailored for individual subjects can be done safely and may improve tolerability.

Table 32 Overall treatment-Emergent Adverse Events (TEAEs) by Treatment Arm (Safety Set)

Category	Ramp-Up Schedule A		Ramp-Up Schedule B		Ramp-Up	No Ramp-Up Schedule C		No Ramp-Up	
	Low TDL (TA 1) (N=8)	High TDL (TA 4) (N=8)	Low TDL (TA 2) (N=8)	High TDL (TA 5) (N=9)	Total (N=33)	Low TDL (TA 3) (N=8)	High TDL (TA 6) (N=10)	Total (N=18)	Overall Total (N=51)
	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m	n (%) m
Any TEAE	8 (100.0) 65	8 (100.0) 82	8 (100.0) 69	9 (100.0) 91	33 (100.0) 307	8 (100.0) 50	10 (100.0) 65	18 (100.0) 115	51 (100.0) 422
Severe TEAE	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Serious TEAE	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
TEAEs leading to Death	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Nonserious TEAE	8 (100.0) 65	8 (100.0) 82	8 (100.0) 69	9 (100.0) 91	33 (100.0) 307	8 (100.0) 50	10 (100.0) 65	18 (100.0) 115	51 (100.0) 422
HYQVIA-related TEAE	8 (100.0) 65	8 (100.0) 82	8 (100.0) 67	9 (100.0) 91	33 (100.0) 305	8 (100.0) 50	10 (100.0) 60	18 (100.0) 110	51 (100.0) 415
HYQVIA Nonrelated TEAE	0 0	0 0	2 (25.0) 2	0 0	2 (6.1) 2	0 0	3 (30.0) 5	3 (16.7) 5	5 (9.8) 7
HYQVIA-related serious TEAE	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Local TEAEs	8 (100.0) 62	8 (100.0) 81	8 (100.0) 67	9 (100.0) 90	33 (100.0) 300	8 (100.0) 48	10 (100.0) 54	18 (100.0) 102	51 (100.0) 402
Systemic TEAE	1 (12.5) 3	1 (12.5) 1	2 (25.0) 2	1 (11.1) 1	5 (15.2) 7	2 (25.0) 2	5 (50.0) 11	7 (38.9) 13	12 (23.5) 20
TEAEs Leading to Disc. from the Study	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0	0 0
Infusion-associated TEAEs	8 (100.0) 65	8 (100.0) 82	8 (100.0) 69	9 (100.0) 91	33 (100.0) 307	8 (100.0) 49	10 (100.0) 57	18 (100.0) 106	51 (100.0) 413
Temporally-associated TEAEs	8 (100.0) 65	8 (100.0) 82	8 (100.0) 69	9 (100.0) 91	33 (100.0) 307	8 (100.0) 49	10 (100.0) 64	18 (100.0) 113	51 (100.0) 420
AR plus suspected AR of interest	8 (100.0) 65	8 (100.0) 82	8 (100.0) 69	9 (100.0) 91	33 (100.0) 307	8 (100.0) 50	10 (100.0) 65	18 (100.0) 115	51 (100.0) 422

Table 33 Summary of Adverse Event Rate (Safety Set)

System Organ Class Preferred Term Category	Ramp-Up Schedule A		Ramp-Up Schedule B		Ramp-Up	No Ramp-Up Schedule C		No Ramp-Up	
	Low TDL (TA 1) (N=8)	High TDL (TA 4) (N=8)	Low TDL (TA 2) (N=8)	High TDL (TA 5) (N=9)	Total (N=33)	Low TDL (TA 3) (N=8)	High TDL (TA 6) (N=10)	Total (N=18)	Overall Total (N=51)
Number of Infusions	33	40	32	31	136	21	17	38	174
Number of Subjects	8	8	8	9	33	8	10	18	51
Subject-Years	0.917	1.177	1.342	1.229	4.665	1.081	0.652	1.733	6.398
Any TEAE									
Number of TEAEs	65	82	69	91	307	50	65	115	422
Per Infusion	1.970	2.050	2.156	2.935	2.257	2.381	3.824	3.026	2.425
Per Subject	8.125	10.250	8.625	10.111	9.303	6.250	6.500	6.389	8.275
Per Subject-Year	70.883	69.669	51.416	74.044	65.809	46.253	99.693	66.359	65.958
Number of HYQVIA-related TEAEs	65	82	67	91	305	50	60	110	415
Per Infusion	1.970	2.050	2.094	2.935	2.243	2.381	3.529	2.895	2.385
Per Subject	8.125	10.250	8.375	10.111	9.242	6.250	6.000	6.111	8.137
Per Subject-Year	70.883	69.669	49.925	74.044	65.380	46.253	92.025	63.474	64.864
Number of HYQVIA-unrelated TEAEs	0	0	2	0	2	0	5	5	7
Per Infusion	0	0	0.063	0	0.015	0	0.294	0.132	0.040
Per Subject	0	0	0.250	0	0.061	0	0.500	0.278	0.137
Per Subject-Year	0	0	1.490	0	0.429	0	7.669	2.885	1.094
Number of Local TEAEs	62	81	67	90	300	48	54	102	402
Per Infusion	1.879	2.025	2.094	2.903	2.206	2.286	3.176	2.684	2.310
Per Subject	7.750	10.125	8.375	10.000	9.091	6.000	5.400	5.667	7.882
Per Subject-Year	67.612	68.819	49.925	73.230	64.309	44.403	82.822	58.857	62.832
Number of Systemic TEAEs	3	1	2	1	7	2	11	13	20
Per Infusion	0.091	0.025	0.063	0.032	0.051	0.095	0.647	0.342	0.115
Per Subject	0.375	0.125	0.250	0.111	0.212	0.250	1.100	0.722	0.392
Per Subject-Year	3.272	0.850	1.490	0.814	1.501	1.850	16.871	7.501	3.126

Post marketing experience

Not applicable.

2.5.1. Discussion on clinical safety

The MAH has supplied a safety database encompassing two trials in CIDP patients (n=100) and one in healthy volunteers (n=51) who were exposed to HyQvia. Mean exposure to HyQvia was 23.4 months. HyQvia demonstrated a favourable safety and tolerability profile in the completed Phase 1 study in healthy volunteers (TAK-771-1001) and in the two CIDP studies (161403 and 161505).

In study 161403, although local and systemic TEAEs occurred more frequently in subjects receiving HyQvia, both severe and serious TEAEs occurred less frequently in the HyQvia group than in the placebo group. The increase in local TEAEs with HyQvia relative to baseline was approximately 3-fold higher than the increase in systemic TEAEs, suggesting that the burden of HyQvia treatment on study subjects mainly relates to local TEAEs. However, 0.3% and 0.2% of infusions were interrupted, stopped or required reduced infusion rates due to intolerability in the verum and placebo group, respectively.

In study 161505, 1.0% of infusions were interrupted, stopped or required reduced infusion rates due to intolerability. Adverse events occurring during or after the infusion were reported in 139 (5.4%) infusions. AEs assessed as related that occurred during or after HyQvia infusion in >5 per 100 infusions included infusion site erythema and infusion site swelling.

In the integrated safety analysis of the CIDP studies (161403 and 161505), 100 patients with CIDP were exposed to HyQvia and followed up for 168.8 patient-years. The mean follow-up time was 14.9 months. Almost all (89/100) CIDP patients experienced TEAEs (0.48 TEAEs per infusion and 15.2 TEAEs per subject), of which 70% experienced TEAEs related to HyQvia treatments. The rate of 27.8 of TEAEs related to HyQvia per 100 infusions was within the range of published rates with other IgG products as well as of the known safety profile of HyQvia. The majority of TEAEs were mild or moderate, local, and/or self-limited and consistent with the known safety profile of HyQvia. The most common temporally-associated or causally-related AEs with HyQvia were headache, pyrexia, and local TEAEs including erythema, infusion site erythema, infusion site oedema, and injection site erythema. There were no very common temporally associated or causally related AEs. The reported rates were consistent across the trials and were within the known safety profile of HyQvia and other IG products. Some common temporally associated systemic TEAEs reported with IVIg administration, such as hemodynamic changes, nausea/vomiting, and flu-like symptoms, were less commonly observed in these studies (CSL Behring, 2022, Hughes et al., 2008, Mendell et al., 2001).

20 SAEs were reported, of which only one SAE was possibly related to HyQvia. This subject developed a stroke within 72 hours of the last dose. The role of HyQvia treatment in the occurrence of carotid occlusion that ultimately led to middle cerebral artery embolism in this subject was not known. However, based on the timely association, the classification as possibly related is appropriate. In the SmPC section 4.4, a special warning for thromboembolism is already included and adequately described. Cerebrovascular accident and Ischaemic stroke has also been added as an ADR in the section 4.8 of the SmPC. Moreover, one death (cholangiocarcinoma) occurred during the studies which was not related to HyQvia. In addition, assessment of haemolysis and other clinical laboratory parameters did not raise any safety concerns with respect to HyQvia administration, and no substantial changes from baseline were observed in the vital signs and physical examinations among the study subjects. There were rare occurrences (by infusion frequency category) of mild reactions of angioedema, allergic dermatitis, drug hypersensitivity, hypersensitivity, and urticaria. No new safety signals were identified. Three subjects experienced thrombotic events, including cerebrovascular accident and ischemic stroke in two subjects with underlying risk factors and thrombophlebitis superficial in the other subject. These figures were within the known range of immunoglobulin preparations. 7 subjects were withdrawn due to AEs.

The tabulated list of ADRs in the SmPC section 4.8 has been updated to include all AEs regardless of their frequency in line with the SmPC template. The frequency of ADRs was also updated based on pooled results from all trials with HyQvia, and common AE of SCIg observed with HyQvia have been added in the table. In addition, frequency of ADR per patient was added in line with the core SmPC.

15 subjects receiving HyQvia developed positive binding anti-rHuPH20 antibodies, one of whom also developed neutralizing antibodies, but neither antibody type was associated with an increased incidence of TEAEs. The rate (15%) was within the range of known prevalence rates (2% - 18% (Rosengren et al., 2015)). AR/SAR rates were similar in subjects with negative antibody titers (34.3 per 100 infusions) compared to subjects with positive antibody titers (26.2 per 100 infusions).

1 subject receiving placebo developed positive binding anti-rHuPH20 antibodies. The information on immunogenicity has been added in section 4.8 of the SmPC.

HyQvia with and without Ramp-Up dosing was safe and well tolerated in healthy volunteers. All TEAEs reported (422 TEAE in 51/51 (100%) subjects) were mild in severity, mostly local and all infusions except for one was tolerated. No TEAE led to early discontinuation. The higher subject dropout rate (50%) and incidence of systemic TEAEs (38.9%) in the No Ramp-Up dosing groups compared to Ramp Up groups (12.1% drop-out; systemic TEAE 15.2%) suggests that tolerability may be improved with Ramp-Up dosing, especially when high doses of HyQvia need to be administered. Thus, the results of the study TAK-771-1001 indicate that the ramp-up dose can be safely administered and may improve tolerability.

In conclusion, the results of the safety analysis show that HyQvia has a favourable safety profile as a maintenance therapy for CIDP.

2.5.2. Conclusions on clinical safety

No new safety concerns have emerged from the completed study 161403 and the ongoing study 161505. Safety data showed that HyQvia doses were well tolerated in CIDP patients. The safety profile was consistent with the approved product information for the marketed product and was within the range of other IgG products. No direct comparison of HyQvia to the safety of other IG preparations is possible, as no head-to head- trials have been performed. Overall, the CHMP concluded that the safety profile of HyQvia in treatment of patients with CIDP is considered acceptable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 14.3 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 14.3 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency.
	Infusion site reactions (infusion site leaking).
	Thromboembolic events (TEEs).
Important potential risks	Drug administration error: incorrect sequence of administration of products.
Missing information	Limited information on safety in pregnant and lactating women.
	Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years.
	Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20.

Pharmacovigilance plan

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
161406 – Non-Interventional Post-Marketing Safety Study on the Long-Term Safety of HyQvia (Global) Ongoing	To evaluate safety data in patients with PID. This study is a post market commitment to the FDA. (US only).	Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20.	Protocol Submission	17-September-2015 (Amendment 2)
			First interim analysis	After 50 subjects have been enrolled
			Last interim analysis	Not later than 6 months before last subject out (LSO)
			Final report	23-August-2023
			EMA submission	Q4 2023
161503* – Efficacy, Safety, Tolerability, Immunogenicity and Pharmacokinetic Evaluation of HyQvia in Paediatric Subjects with Primary Immunodeficiency	*Primary Objective:* Safety of HyQvia treatment in paediatric subjects with PIDD who have received prior IV or SC immunoglobulin therapy before	Limited information on long-term treatment in patients under the age of 18 years. Limited clinical data on the potential for long-term local and	Final report	2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Diseases. (US study).	enrolment into the study. *Secondary Objective:* Further safety assessments (e.g., immunogenicity), tolerability, characteristics of product administration, treatment preference and satisfaction, health-related quality of life, efficacy (immunoglobulin G trough levels), and PK parameters.	systemic reactions related to potential antibody development against recombinant human hyaluronidase in the paediatric population.		

Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	**Routine risk minimisation measures:** SmPC Section 4.3 SmPC Section 4.4 and PL section 4 where advice given to train the patients to detect early signs of hypersensitivity reactions and monitor the patients throughout the infusion period. SmPC Section 4.8 PL Section 2 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Immunological Event Questionnaire. **Additional pharmacovigilance activities:** None
Important identified risks: Infusion site reactions (infusion site leaking)	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 PL Section 2 PL Section 4 SmPC Section 4.4 and PL section 3 contains advice to use longer needles and/or more than one infusion site to avoid infusion site leakage. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Leakage or site leaking questionnaire. **Additional pharmacovigilance activities:** None.
Important identified risks:	**Routine risk minimisation**	**Routine pharmacovigilance**

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Thromboembolic events (TEEs)	**measures:** SmPC Section 4.4 where advice is given to monitor the patient for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity and patients should be sufficiently hydrated before use of immunoglobulins. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.	**activities beyond adverse reactions reporting and signal detection:** Expedited reporting of all TEEs. TEE questionnaire. **Additional pharmacovigilance activities:** None.
Important potential risks: Drug administration error - incorrect sequence of administration of products	**Routine risk minimisation measures:** SmPC Section 2 SmPC Section 4.2 contains the recommended infusion rate. SmPC Section 4.4 where advice is given on monitoring and management of adverse reaction. PL Section 3 PL Section 6 **Additional risk minimisation measures:** Educational materials	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing information: Limited information on safety in pregnant and lactating women	**Routine risk minimisation measures:** SmPC Section 4.6 and PL Section 2 where fertility, pregnancy and lactation are discussed. **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Missing information: Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.6 SmPC Section 4.8 SmPC Section 5.1 SmPC Section 5.2 PL Section 2 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** Study 161503 (Category 3)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information: Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20	**Routine risk minimisation measures:** SmPC Section 4.4 SmPC Section 4.8 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Immunological Event Questionnaire. **Additional pharmacovigilance activities:** Study 161406 (Category 3) Study 161503 (Category 3)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1 and 5.2 and 6.6 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current QRD template and core SmPC guideline, which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of United Kingdom (Northern Ireland).

Editorial changes are also made to the PI that do not change the content of the previously approved Product Information.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: the changes affecting the SmPC, which are also reflected in Patient Leaflet, are considered minor in nature.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

CIDP is a rare, debilitating, chronic autoimmune disorder that affects the peripheral nerves' myelin sheath, resulting in progressive symmetric weakness and impaired sensory function in the arms and legs.

Worldwide estimates of the prevalence of CIDP range from 1.9 to 8.9 per 100,000 with an annual incidence of 0.15 to 1.6 per 100,000 (Broers et al., 2019, Iijima et al., 2008, Laughlin et al., 2009, Lunn et al., 1999, McLeod et al., 1999, Mygland and Monstad, 2001).

Although the exact etiology is unknown, CIDP is considered an immune-mediated disorder characterized by inflammatory changes and infiltration of macrophages and T-cells in the myelin sheath of the nerves. Chronic inflammation results in demyelination, remyelination, and onion bulb formation. Long-term demyelination leads to axonal loss. The amount of axonal loss determines the level of disability and long-term prognosis (Koller et al., 2005, Ulane and Brannagan, 2012).

3.1.2. Available therapies and unmet medical need

IVIgs or corticosteroids are recommended first-line treatments for CIDP patients. IVIg is an effective treatment for CIDP and is used for both induction and maintenance therapy. Both IVIg and SCIg are recommended maintenance treatments in adult CIDP patients.

In general, SCIg is generally better tolerated than IVIg, require no venous access, enables shorter infusion time and the option for at-home self-infusion. However, conventional SCIg treatment only allows for delivery of a limited volume of IGI into the SC tissue, necessitating the use of multiple infusion sites, multiple needle insertions, and frequent administration (weekly rather than monthly). SCIg also has lower bioavailability than IVIg (65-67%) and requires a higher monthly total IgG dose.

HyQvia has been developed to leverage the advantages and address the shortfalls of both IVIg and SCIg. HyQvia enables administration of large volumes of IgG into the SC tissue, thus reducing the number of infusion sites, needle sticks, infusion times, and infusion frequency. HyQvia provides comparable trough levels and bioavailability to IVIg, thereby allowing for administration at up to 4-week intervals. SCIg do not require vascular access or travel to infusion centres. Systemic infusion reactions such as hemodynamic alterations, hypersensitivity reactions, and flu-like symptoms occur infrequently. Such advantages are expected to result in improved patient adherence and better outcomes for patients with CIDP. Furthermore, it is desirable to have additional approved products for CIDP in the event of a recall and/or shortage.

3.1.3. Main clinical study

The safety and efficacy of HyQvia as a maintenance therapy for CIDP has been evaluated in one completed interventional study (161403) and one ongoing study (161505 for which an iCSR is available). The PK study TAK-771-1001 provides further information on the dosing regimen for HyQvia.

Study 161403 was a Phase 3, prospective, multicentre, double-blind, randomised, placebo-controlled study to evaluate the efficacy, safety, and tolerability of HyQvia and IGI (Human), 10% (GGL/KIOVIG) for the treatment of CIDP. The study enrolled adult subjects with a confirmed diagnosis of CIDP who had remained on a 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 IVIg therapy for at least 12 weeks prior to screening.

The study consisted of two parts: Epoch 1 of the study was double-blind and placebo-controlled. Eligible subjects were randomised in a 1:1 ratio to receive either HyQvia or the 0.25% albumin placebo solution with rHuPH20 in a double-blind fashion for a period of 6 months or until relapse. The dosing regimen for HyQvia or 0.25% albumin placebo with rHuPH20 was the same as the subject's pre-randomisation monthly equivalent immunoglobulin G (IgG) dose (or at matching infusion volume for subjects in the placebo group) when administered at a dosing frequency of every 2, 3, or 4 weeks. A dose ramp-up schedule was employed until the subject's full dose was reached. In Epoch 2, open-label treatment with IVIg was provided to any subject (regardless of their treatment assignment in Epoch 1) who met the definition of relapse during Epoch 1 and agreed to Epoch 2, in order to restore functional ability.

In this procedure, only Epoch 1 is evaluated, since Epoch 2 does not include HyQvia treatments.

3.2. Favourable effects

The analysis of the primary endpoint of the study 161403 shows a significantly lower CIDP relapse rate in the MITT population in the HyQvia group compared to placebo (9.7% vs 31.4%, p=0.0045), when missing relapse determinations are imputed as no relapse. The estimated treatment difference of 21.8% indicates that HyQvia is more effective than placebo in preventing relapse of neuromuscular disability and impairment in CIDP. The efficacy of HyQvia is supported by predefined analyses using alternative definitions of relapse and alternative outcome scales.

Initially, missing values not explained in detail and intercurrent events with unknown (or undefined) influence on the development of a relapse occurred and gave rise to some uncertainties regarding the

magnitude and interpretation of the primary (and important secondary) endpoints. Refined definitions of a suitable estimand and according analyses were submitted as requested by the CHMP. The MAH has defined the ICEs with corresponding strategies such that for example treatment discontinuation due to CIDP worsening would be addressed with a composite strategy and thus these patients were considered as "relapse" in the analysis. Missing values were also imputed depending on the reason for missingness. The revised primary analysis resulted in a relapse rate of 31.7% (95% CI: 21.96, 43.39) vs. 15.5% (95% CI: 8.36, 26.84) for the Placebo and HyQvia arm (treatment difference -16.2% (95% CI: -29.92; -1.27%)). Results provided in the sensitivity analyses showed consistent results with the revised primary analysis. Given the nature of the reasons for missings or early discontinuation, the revised primary analysis provide a more reasonable estimate for the relapse rates than the original primary analysis. The applicant updated the SmPC accordingly with the revised estimates.

Positive differences between HyQvia and placebo in favour of HyQvia were seen in the time to relapse, INCAT score, R-ODS score and grip strength, resulting in a lower number of subjects treated with HyQvia experiencing a worsening of functional disability in Epoch 1 compared to subjects receiving placebo (37.5% vs 54.4%, p=0.0896). Overall, HyQvia led to stabilisation and improvement in activities of daily living and quality of life, as indicated by higher scores in the PROs, in contrast to deterioration in subjects receiving placebo.

Preliminary data on the durability of efficacy of HyQvia in CIDP are provided with the interim analysis of the ongoing extension study 161505. There, 7.9% of subjects relapsed, of which 4 out of 5 received already HyQvia in the pivotal study, and only one subject was on placebo before. Pooled data from both studies show that a total of 10/100 subjects (10%) relapsed over a total follow up of 194.7 patient-years, resulting in a 6-month relapse rate of 2.6%-7.4% (depending on the imputation of missing relapse determinations in the analysis). In addition, scores assessing worsening of functional disability remain relatively stable over time. This suggests that HyQvia maintains a stable disease course over time.

Other benefits of HyQvia include the administration of large volumes of IgG into the SC tissue, minimizing the number of infusion sites, needle sticks, and infusion times, as compared to other available SC treatment options. Monthly SC administration of HyQvia results in stable mean serum trough levels of total IgG that are comparable to IVIg and higher levels than in subjects receiving placebo. There is no correlation between serum trough IgG levels and the occurrence of relapses. These benefits are also reflected in higher rates of treatment satisfaction and effectiveness with HyQvia compared to placebo in subjects in the study 161403 Epoch 1. Moreover, HyQvia does not require vascular access, which may facilitate administration outside of infusion centres, increasing patient convenience. Analysis of the treatment preference questionnaire shows that more than two thirds of subjects prefer HyQvia to their pre-study IVIg and find it more convenient. The majority of subjects would choose to continue receiving HyQvia.

Finally, a gradual increase in HyQvia dose and time intervals may help patients to adjust to the large SC doses while becoming comfortable with HyQvia administration. Indeed, the results of the study TAK-771-1001 and 161403 suggest that a dose ramp-up tailored to the individual subject can be safely done, can result in stable IgG trough levels and can improve tolerability.

3.3. Uncertainties and limitations about favourable effects

In CIDP patients, it is recommended that IVIG doses be periodically tapered to assess the continued need for therapy. If symptoms return after IG withdrawal, treatment is restarted (GL: van den Bergh et al., 2021). For clinical studies, it has been emphasized that only participants who have deteriorated after IVIG withdrawal should be randomised to ensure that they require the reintroduction of treatment. However, no IVIg withdrawal period prior to treatment with HyQvia was included in Epoch 1. In other studies, such as the study IgPro20_3003, ICE study or study IgPro10_3001, subjects had to be IVIG-free for at least 3 months or had to be washed out of IVIG. Therefore, it is not known how many subjects in total and in which cohort (verum or placebo) these subjects were enrolled. This is particularly of

important information, as the relapse rates were considerably lower in both the verum and placebo group (15.5% and 31.7%) compared to conventional SCIg (33%/39% for SCIg doses and 63% for placebo). Importantly, 68.3% of subjects in the placebo arm of the study 161403 Epoch 1 showed no worsening within 24 weeks, which was a higher number than observed in the PATH study (van Schaik et al, 2018; 37% on placebo did not relapse) and higher than the number of subjects expected to no longer require maintenance IVIg treatment (29-45%, Rabin et al, 2014; Viala et al, 2010).

In the Scientific Advice in 2015, 7% of subjects on HyQvia and 25% on placebo were expected to relapse in Epoch 1. These were slightly lower than the numbers seen in Epoch 1 and lower than other studies. Of note, in contrast to previous CIDP trials (Hughes et al., 2018, Hughes et al., 2008, van Schaik et al., 2018) which used a single INCAT-based relapse definition, study 161403 required a second INCAT assessment to confirm the diagnosis of relapse. This stricter definition of relapse may have also contributed to the lower numbers of relapses in study 161403. In addition, the carry-over effect of IVIG pre-treatment lasts up to 10 weeks after starting HyQvia, which is almost half the duration of Epoch 1. This is also reflected over time in the assessment of serum trough IgG levels in Epoch 1, in which levels initially remain stable from baseline/pre-study IVIg and then decline at week 15 on HyQvia.

Overall, the potential inclusion of subjects in remission together with the carry-over effects from previous IVIg treatment may have led to an overestimation of the efficacy of HyQvia in preventing relapses in CIDP. Possible reasons for the reduction in the serum trough IgG levels and a discussion of the relationship between these levels and the clinical outcome have been provided by the MAH and are considered acceptable by the CHMP.

The evidence for the efficacy of SCIg as an induction therapy is currently very limited (only one randomised controlled crossover study in 20 patients (Markvardsen et al, 2017)), and induction therapy in CIDP patients is restricted to IVIg. Therefore, the MAH updated the indication to mention that HyQvia is only approved for maintenance therapy in CIDP after IVIg stabilization, as study 161403 only enrolled CIDP patients on stable IVIg treatment.

The long-term beneficial effects of maintenance treatment with HyQvia cannot be fully predicted, as only interim results from the extension study 161505 are available. 4 out of 5 subjects who relapsed in the extension study had already received HyQvia in Epoch 1, while only one subject who had previously received placebo relapsed. This may indicate that dose adjustments are required for preventing relapses. Deterioration in functional ability scores appeared to be relatively stable, with clinically insignificant fluctuations in subjects receiving HyQvia. Final results from the expansion study 161505 are awaited and will be submitted by April 2024 and will provide long-term data.

None of the trials included paediatric subjects, so there is some uncertainty about the magnitude of the beneficial effects of s.c. treatment with HyQvia in the maintenance treatment of children with CIDP. However, adequate justification for the extrapolation to the paediatric population was provided by the MAH and the PI was updated accordingly.

To date, there have been no head-to-head trials in patients with CIDP in which the relapse rates of maintenance therapy with IVIg and SCIg have been compared. Therefore, the optimal serum trough IgG levels required for stable disease and whether SCIg are really as effective as IVIg remain open. The MAH provided a statement in the SmPC to highlight that dose modifications or reductions may be appropriate depending on the individual patient's clinical response.

3.4. Unfavourable effects

In study 161403, higher rates of total/local/systemic AR/SARs were seen in the HyQvia group than in the placebo group. However, more subjects in the placebo group experienced serious or severe ARs.

Including the extension study, 100 patients with CIDP were followed up for in 168.8 patient-years. The mean follow-up time was 14.9 months. The most common temporally-associated or causally-related AEs with HyQvia were headache, pyrexia, and local TEAEs including erythema, infusion site erythema, infusion

site oedema, and injection site erythema. There were no very common temporally associated or causally related AEs. The reported rates were consistent across the three trials. Of note, the incidence of systemic ARs was lower than that typically observed with IVIG. The majority of TEAEs were mild to moderate, self-limited, and did not require discontinuation of infusions. In study 161403, 0.3% and 0.2% of infusions were interrupted, stopped or required reduced infusion rates due to intolerability in the verum and placebo group, respectively. In study 161505, 1.0% of infusions were interrupted, stopped or required reduced infusion rates due to intolerability. Adverse events occurring during or after the infusion were reported in 139 (5.4%) infusions. AEs assessed as related that occurred during or after HyQvia infusion in >5 per 100 infusions included infusion site erythema and infusion site swelling.

The overall incidence of AEs in both CIDP studies (in 89% of subjects, 0.48 TEAEs per infusion and 15.2 TEAEs per subject) was within the range of other IGs and consistent with the known safety profile of HyQvia. One death was reported that was not related to study treatment. Key risks with HyQvia and immunoglobulins in general are allergic/hypersensitivity reactions and thromboembolic events. In the CIDP studies, these events were rare and included mild hypersensitivity reactions (angioedema, dermatitis allergic, drug hypersensitivity, hypersensitivity, and urticarial) and three thrombotic events, cerebrovascular accident and ischemic stroke in two subjects with underlying risk factors and thrombophlebitis superficial in the other subject. No new safety signals were identified. In conclusion, the use of HyQvia for the treatment of CIDP is not expected to change the safety profile.

The tabulated list of ADRs in the SmPC section 4.8 has been updated to include all AEs regardless of their frequency in line with the SmPC template. The frequency of ADRs was also updated based on pooled results from all trials with HyQvia, and common AE of SCIg observed with HyQvia have been added in the table. In addition, frequency of ADR per patient was added in line with the core SmPC.

In study TAK-771-1001, HyQvia with and without Ramp-Up dosing was safe and well tolerated in healthy volunteers. The higher subject dropout rate and incidence of systemic TEAEs in the high TDL-No Ramp-Up dosing group compared to all other treatment groups suggests that tolerability may be improved with Ramp-Up dosing, especially when high doses of HyQvia need to be administered. Ramp-up dosing is therefore recommended to improve tolerability.

3.5. Uncertainties and limitations about unfavourable effects

Due to the long follow-up in study 161505, AE rates per subject are rather high and should be viewed in the context of the long follow-up period. The rates of TEAEs per infusion are within the range of IGs and within the known safety profile of HyQvia.

A definite analysis of the long-term safety and tolerability is not provided with this submission, as only interim results from the extension study 161505 are available, final results will be submitted in April 2024. However, the data as provided with this application, as well as what is known about other IVIgs/SCIgs in the treatment of CIDP, do not indicate a relevant change in the safety profile.

As there has been no head-to-head studies in patients with CIDP comparing HyQvia with other IVIg/SCIg, no conclusions can be drawn about the safety and tolerability of HyQvia in relation to other IGs.

3.6. Effects Table

Table 34 Effects Table for HyQvia in CIDP

Effect	Short description	Unit	HyQvia	placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
CIDP relapse rate (revised)	Percentage of subjects who had CIDP relapse	%	15.5%	31.7%	Treatment difference of -16,2% (95% CI: -29.92%; -1.27%)	Study 161403
Worsening of functional disability	Percentage of subjects who experienced a worsening of functional disability	n/%	21/56 (37.5%)	37/68 (54.4%)	Treatment difference of -16.9% (p=0.0896) Uncertainties due to missing values	Study 161403
Unfavourable Effects						
Serious AEs	Serious AEs related to IP	n/%/number of events	1/1.6%/1	5/7.1%/5		Study 161403
AESI	allergic reactions, local and systemic immune complex mediated reactions, and thrombotic and embolic events	n/%/number of events	2/3.2%/2	-	Events were infusion site induration and cerebrovascular accident	Study 161403

Abbreviations: CIDP=Chronic Inflammatory Demyelinating Polyradiculoneuropathy, AE=adverse events, AESI=adverse events of special interest, IP=investigational product, CSR=completed study report

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The therapeutic efficacy of IVIg and SCIg as induction (and maintenance) treatments in patients with CIDP is well established and the 2021 EFNS/PNS guidelines recommend IgG as the first-line treatment in CIDP. The studies (TAK-771-1001, 161403, 161505) included in this submission add to the existing knowledge by showing that HyQvia is a safe, tolerable, and effective form of IgG maintenance treatment in CIDP patients.

Treatment with HyQvia resulted in a significant reduction in CIDP relapse compared to placebo. CIDP relapse was based on the adjusted INCAT score, which has been used previously in CIDP studies. The 10-point INCAT score is a globally recognised, validated and reliable disability scale. A change of one point in the INCAT score is considered clinically meaningful.

As only IVIg-stabilized subjects were enrolled, the extension of indication only substantiates maintenance treatment of CIDP after prior IVIg treatment at this time.

Secondary efficacy endpoints analysed in this study also revealed positive differences between HyQvia and placebo and included commonly used scores to assess disease progression (R-ODS, mean grip strength, MRC). Thus, SC treatment with HyQvia was shown to be effective in the maintenance treatment of CIDP. Considering the additional burden of CIDP relapse on functional capacity and disease progression, the reduction in relapse risk and improvement in functional capacity with HyQvia is considered clinically relevant. Patient-reported outcomes indicated that HyQvia treatments may increase treatment compliance.

Uncertainties remain regarding the overlapping effect of prior IVIg treatment and the potential inclusion of CIDP patients in remission. With regard to long-term efficacy and safety, results from the extension study 161505, which enrolled subjects who completed study 161403, will be provided in April 2024 and will provide further information on the clinical efficacy and safety of HyQvia in CIDP patients.

In general, HyQvia had an acceptable safety profile in the maintenance treatment of CIDP. The most common AEs were local reactions, and causally related AEs included headache and fatigue. The majority of AEs were mild to moderate in severity and manageable and common to IG preparations. Only one SAE of cerebrovascular accident was considered related to HyQvia treatment. Overall, the safety profile was similar to that seen in other indications and no new safety signals were identified.

Ramp-Up dosing is recommended when switching to HyQvia as this may improve tolerability and is associated with fewer adverse events. The dose and treatment intervals required to achieve and maintain a clinical response may vary widely between individuals. Dose adjustments may be required and dose reductions should be periodically tested.

Overall, efficacy endpoints are clinically relevant and showed favourable effects in CIDP patients with an acceptable safety profile.

3.7.2. Balance of benefits and risks

The Study 161403 evaluated HyQvia in the maintenance treatment of CIDP and demonstrated a clinically and statistically relevant reduction in CIDP relapse rate based on the adjusted INCAT score. The safety profile of HyQvia was consistent with the previously reported safety profile of HyQvia and is comparable to other IG preparations. Overall, based on the efficacy results of clinical trials and accumulated pharmacovigilance data, the benefit-risk balance of HyQvia for maintenance therapy in patients with CIDP is considered positive.

3.8. Conclusions

The overall B/R of HyQvia is positive in the following indication:

Immunomodulatory therapy in adults, children and adolescents (0 to 18 years) in:

• Chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilization with IVIg.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension of indication to include treatment of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) as maintenance therapy after stabilization with IVIg in adults, children and adolescents for HyQvia, based on final results from studies 161403 and TAK-771-1001; and interim results from study 161505. 161403 and 161505 are interventional Phase III efficacy and safety studies, while TAK-771-1001 is an interventional Phase I safety study. As a consequence, sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1,5.2 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. Version 14.3 of the RMP has also been accepted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template.

The variation leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, IIIA and IIIB and to the Risk Management Plan are recommended.