EU RISK MANAGEMENT PLAN (RMP)

for

HyQvia (Human Normal Immunoglobulin)

RMP Version number: 16.0

Date: 31-July-2024

[redacted]

European Union Risk Management Plan (RMP) for HyQvia (Human Normal Immunoglobulin)

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 16.0

Data lock point (DLP) for this RMP: 31-May-2024

Date of final sign off: 31-July-2024

Rationale for submitting an updated RMP: The Risk Management Plan is updated to consolidate the European Union (EU) RMP versions 14.3 and 15.0 and the DLP was updated to 31-May-2024. Additionally, healthy volunteers have been removed from the tables in section "Part II: Module SIII - Clinical trial exposure" since they do not belong to any disease category.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Updated the section as per approved Summary of Product Characteristics (SmPC).
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	Not applicable.
• **Module SII Non-clinical part of the safety specification**	Not applicable.
• **Module SIII Clinical trial exposure**	Updated the clinical trial exposure as per the DLP. Additionally, healthy volunteers have been removed from the tables in section "Part II: Module SIII - Clinical trial exposure" since they do not belong to any disease category.
• **Module SIV Populations not studied in clinical trials**	SIV.2 and SIV.3 were updated in alignment with the updated clinical trial exposure data included in Module SIII.
• **Module SV Post-authorisation experience**	Updated the exposure as of DLP.
• **Module SVI Additional European Union (EU) requirements for the safety specification**	Not applicable.
• **Module SVII Identified and potential risks**	Provided justification for the re-wording of missing information from "Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20" to "Limited clinical data on the influence of the type of PID and CIDP on the immunogenicity of rHuPH20" to include PID and CIDP indications.
• **Module SVIII Summary of the safety concerns**	Re-worded the missing information as stated in Module SVII.
Part III Pharmacovigilance plan	Re-worded the missing information as stated in Module SVII

[redacted]

[redacted]

RMP Module:	Significant Changes:
Part IV Plans for post-authorisation efficacy studies	Not applicable.
Part V Risk minimisation measures	Re-worded the missing information as stated in Module SVII
Part VI Summary of the risk management plan	Re-worded the missing information as stated in Module SVII
Part VII Annexes	Annex 8: Updated summary of changes to the risk management plan over time.

Other RMP versions under evaluation:

RMP Version number: Not applicable

Submitted on: Not applicable

Procedure number: Not applicable

Details of the currently approved RMP:

Version number: 14.3 and 15.0

Approved with procedure: EMEA/H/C/002491/II/0087 (v14.3) and EMEA/H/C/002491/II/0096 (v15.0)

Date of approval (opinion date): 25-January-2024 (v14.3) and 16-May-2024 (v15.0)

QPPV name: Jean-Marie Heim, MD

Please note that e-signature may also be performed by [redacted] Deputy EUQPPV, [redacted]. Deputy EUQPPV or [redacted] Deputy EUQPPV, on behalf of the EU QPPV (i.e., 'per procurationem').

QPPV signature: [redacted] RMP signatures are kept on file.

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List of Abbreviations

Abbreviation	Definition/Description
ADR	Adverse Drug Reaction
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
AMS	Aseptic Meningitis Syndrome
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
BW	Body Weight
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	The Committee for Medicinal Products for Human Use
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
CLcr	Creatinine Clearance
CLL	Chronic lymphocytic leukaemia
CML	Chronic Myelogenous Leukaemia
CSR	Clinical Study Report
CVID	Common Variable Immunodeficiency
DLP	Data Lock Point
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESID	European Society for Immunodeficiencies
EU	European Union
FcRn	Neonatal Crystallizable Fragment Receptor
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practice
HBV	Hepatitis B Virus
HCP	Healthcare Professionals
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HSCT	Hematopoietic Stem Cell Transplantation
IDEaL	Immunoglobulin Diagnosis, Evaluation, and key Learnings
IG	Immunoglobulins
IG 10%	Immune Globulin Infusion (Human) 10%, administered IV or SC

Abbreviation	Definition/Description
IgA	Immunoglobulin A
IgAD	Immunoglobulin A Deficiency
IgG	Immunoglobulin G
IGIV 10%	Immune Globulin Intravenous (Human) 10%, administered IV
IgM	Immunoglobulin Macroglobulinemia (M)
IGSC 10%	Immune Globulin Subcutaneous (Human) 10%
ISG	Immune Serum Globulin
ITP	Immune Thrombocytopenia
IV	Intravenous(ly)
IVIg	Intravenous Immunoglobulin
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MGUS	Monoclonal Gammopathy of Undetermined Significance
MI	Myocardial Infarction
MM	Multiple Myeloma
NAb	Neutralizing Antibody
NICHD	National Institute of Child Health and Human Development
NOAEL	No Observed Adverse Effect Level
NZW	New Zealand White
OD	Odds Ratio
PCR	Polymerase Chain Reaction
PID	Primary Immunodeficiency
PIDD	Primary Immunodeficiency Diseases
PL	Package Leaflet
PND	Postnatal Day
PRAC	The Pharmacovigilance Risk Assessment Committee
PSAF	Proven Specific Antibody Failure
PSUR	Periodic Safety Update Report
rHuPH20	Recombinant Human Hyaluronidase
RMP	Risk Management Plan
SC	Subcutaneous(ly)
SCIg	Subcutaneous Immunoglobulin
SID	Secondary Immunodeficiencies
SmPC	Summary of Product Characteristics

Abbreviation	Definition/Description
SMQ	Standardised MedDRA Queries
TEAE	Treatment-Emergent Adverse Event
TEE(s)	Thromboembolic Event(s)
TK	Toxicokinetic(s)
TVR	Triple Virally Reduced
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Human Normal Immunoglobulin
Pharmacotherapeutic group(s) (ATC Code)	J06BA01
Marketing Authorisation Holder	Baxalta Innovations GmbH (a wholly owned subsidiary of Takeda Pharmaceutical Company Limited) Industriestrasse 67 A 1221 Vienna, Austria.
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	HyQvia 100 mg/mL solution for infusion for subcutaneous (SC) use
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Immune sera and immunoglobulins: immunoglobulins, normal human, for extravascular administration
	Summary of mode of action: The IG 10% component provides the therapeutic effect of this medicinal product. The rHuPH20 facilitates the dispersion and absorption of IG 10%. Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of opsonising and neutralizing 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. Recombinant human hyaluronidase is a soluble recombinant form of human hyaluronidase that increases the permeability of the subcutaneous tissue by temporarily depolymerizing hyaluronan. Hyaluronan is a polysaccharide found in the intercellular matrix of the connective tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a very fast turnover with half-life of approximately 0.5 days. The rHuPH20 of HyQvia acts locally. The effects of the hyaluronidase are reversible, and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

	Important information about its composition: Human normal immunoglobulin (IG 10%) vial Glycine Water for injections Recombinant human hyaluronidase (rHuPH20) vial Sodium chloride Sodium phosphate dibasic Human albumin Ethylenediaminetetraacetic acid (EDTA) disodium Calcium chloride Sodium hydroxide (for pH adjustment) Hydrochloric acid (for pH adjustment) Water for injections
Hyperlink to the Product Leaflet (PL)	ema-combined-h-2491-en
Indication(s) in the EEA	Current: Replacement therapy in adults, children and adolescents (0-18 years) in: • Primary immunodeficiency (PID) syndromes with impaired antibody production • Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/L. *PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines. Immunomodulatory therapy in adults, children and adolescents (0 to 18 years) in: • Chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilization with intravenous immunoglobulin (IVIg).
	Proposed: Not applicable.
Dosage in the EEA	Current: The dose and dosage regimen are dependent on the indication. The dose may need to be individualized for each patient dependent on the pharmacokinetic (PK) and clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients. The following dose regimens are given as a guideline. *Replacement therapy in PID* *Patients naïve to immunoglobulin therapy* The dose required to achieve a trough level of 6 g/L is of the order of 0.4 to 0.8 g/kg body weight per month. The dose interval to maintain steady-state levels varies from 2-to-4 weeks. IgG trough levels should be measured and assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dose and aim for higher IgG trough levels (> 6 g/L).

	At the initiation of therapy, it is recommended that the treatment intervals for the first infusions be gradually prolonged from a 1-week dose to up to a 3- or 4-week dose. The cumulative monthly dose of IG 10% should be divided into 1-week, 2-week etc. doses according to the planned treatment intervals with HyQvia. *Patients previously treated with IVIg* For patients switching directly from IVIg, or who have a previous IVIg dose that can be referenced, the medicinal product should be administered at the same dose and at the same frequency as their previous IVIg treatment. If patients were previously on a 3-week dosing regimen, increasing the interval to 4-weeks can be accomplished by administering the same weekly equivalents. *Patients previously treated with subcutaneous immunoglobulin (SCIg)* The initial dose of the medicinal product is the same as for SCIg treatment but may be adjusted to 3 - or 4-weeks interval. The first infusion should be given one week after the last treatment with the previous immunoglobulin. *Replacement therapy in SID* The recommended dose is 0.2 to 0.4 g/kg every 3 -to -4 weeks. IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection; a dose decrease can be considered when the patient remains infection free. *Immunomodulatory therapy in CIDP* Before initiating therapy, the weekly equivalent dose should be calculated by dividing the planned dose by the planned dose interval in weeks. The typical dosing interval range for HyQvia is 3 -to 4 - weeks. The recommended subcutaneous dose is 0.3 to 2.4 g/kg body weight per month, administered in 1-or 2-sessions over 1-or 2-days. The patient's clinical response should be the primary consideration in dose adjustment. The dose may need to be adapted to achieve the desired clinical response. In clinical deterioration, the dose may be increased to the recommended maximum of 2.4 g/kg monthly. If the patient is clinically stable, periodic dose reductions may be needed to observe whether the patient still needs IG therapy. A titration schedule that permits gradual dose increase over time (ramp-up) is recommended to ensure the patient's tolerability until the full dose is reached. During the titration schedule, the calculated HyQvia dose and recommended dose intervals must be followed for the first and second infusions. Depending on the treating physician's discretion, in patients who tolerate the first 2 infusions well, subsequent infusions may be administered by gradually increasing doses and dose intervals, considering the volume and total infusion time. An accelerated titration schedule may be considered if the patient tolerates the SC infusion volumes and the first 2 infusions. Doses less than or equal to 0.4 g/kg may be administered without a titration schedule, provided acceptable patient tolerance. Patients must be on stable doses* of IVIg. Before initiating therapy with the medicinal product, the weekly equivalent dose should be calculated by dividing the last IVIg dose by the IVIg dose interval in weeks. The starting dose and dosing frequency are the same as the patient's previous IVIg treatment. The typical dosing interval for HyQvia is 4-weeks. For patients

[redacted]

	with less frequent IVIg dosing (greater than 4-weeks), the dosing interval can be converted to 4-weeks while maintaining the same monthly equivalent IgG dose. As shown in the table below, the calculated one-week dose (1st infusion) should be administered 2 weeks after the last IVIg infusion. One week after the first dose, the next weekly equivalent dose (2nd infusion) should be administered. A titration schedule can take up to 9 weeks (Table 1), depending on the dosing interval and tolerability. *Variations in the dosing interval of up to ±7 days or monthly equivalent dose amount of up to ±20% between the subject's IgG infusions are considered a stable dose. **Table 1: Recommended IVIg to HyQvia Infusion Dose Titration Schedule**

Week *	Infusion Number	Dose Interval	Example for 100 g every 4 weeks
1	*No infusion*		
2	1st infusion	1-week-dose	25 g
3	2nd infusion	1-week-dose	25 g
4	3rd infusion	2-week-dose	50 g
5	*No infusion*		
6	4th infusion	3-week-dose	75 g
7	*No infusion*		
8	*No infusion*		
9	5th infusion	4-week-dose	100 g (Full dose reached)

	*1st infusion starts 2 weeks after the last IVIg dose. Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: Pharmaceutical form - Solution for infusion HyQvia is a dual vial unit consisting of one vial of human normal immunoglobulin (Immune Globulin 10% or IG 10%) and one vial of recombinant human hyaluronidase (rHuPH20). Human normal immunoglobulin (SCIg)* One mL contains 100 mg of Human normal immunoglobulin (purity of at least 98% IgG). Each vial of 25 mL contains: 2.5 g of human normal immunoglobulin. Each vial of 50 mL contains: 5 g of human normal immunoglobulin. Each vial of 100 mL contains: 10 g of human normal immunoglobulin. Each vial of 200 mL contains: 20 g of human normal immunoglobulin. Each vial of 300 mL contains: 30 g of human normal immunoglobulin The maximum IgA content is 140 micrograms/mL. *Produced from the plasma of human donors.

[redacted]

[redacted]

	Recombinant human hyaluronidase (rHuPH20) One mL contains 160 units of Recombinant human hyaluronidase. Each vial of 1.25 mL contains: 200 units of recombinant human hyaluronidase. Each vial of 2.5 mL contains: 400 units of recombinant human hyaluronidase. Each vial of 5 mL contains: 800 units of recombinant human hyaluronidase. Each vial of 10 mL contains: 1600 units of recombinant human hyaluronidase. Each vial of 15 mL contains: 2400 units of recombinant human hyaluronidase.
	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

[redacted]

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Primary immunodeficiency syndromes	
Incidence	Primary immunodeficiency diseases (PIDD) are recognised as inherited, heterogeneous disorders of the immune system that result in increased rates of severe infections, immune dysregulation associated with autoimmune diseases, and the development of malignancies [redacted]. The International Union of Immunological Societies Expert Committee on Primary Immunodeficiencies currently recognises more than 480 PID syndromes, and more than 480 gene defects causing PID [redacted]. However, some forms of PIDD are extremely rare, so fewer than 20 types comprise more than 90% of all PIDDs [redacted]. The estimated incidence of PIDD (in aggregate) has historically been reported as between as 1 per 10,000 persons and 1 per 50,000 persons[redacted] but with improved definition of clinical phenotypes the collective incidence has been re-estimated to be at least 1 per 1000 to 1 per 5,000 persons[redacted].
Prevalence:	Many studies, based on different methodologies, have attempted to estimate the prevalence of PIDD in various countries and have generated inconsistent results. For example, the most recent estimates obtained were 6.87/100,000 inhabitants in France in 2017 [redacted], 5.6/100,000 in Australia in 2007[redacted], 5.9/100,000 in the United Kingdom (UK) [redacted], and 2.72/100,000 in Germany[redacted], and 1.3/100,000 in Russia [redacted]. These estimates of prevalence were based on data from registries and seem to be much lower than recently reported estimates based on specific population surveys in the United States (US). A US national probability sample conducted in 2005 suggested a population prevalence of diagnosed PID at approximately 1 in 1,200 individuals (86.3/100 000 inhabitants), whereas earlier estimates placed the prevalence at 1 in 10,000 [redacted]. Prevalence estimates derived from administrative medical claims databases estimated US prevalence at between 41.1 and 50.5 per 100 000 [redacted]. Even so, the frequency of specific PID syndromes varies widely. Rare immune deficiencies, such as severe combined immunodeficiency (SCID), occur once in every 100,000 to 500,000 births[redacted] and common variable immunodeficiency (CVID) incidence is approximately 2 per 100,000 [redacted]. Selective Immunoglobulin A (IgA) deficiency (IgAD) can affect as many as 1 in 143 people [redacted]. Highlighting the variability in distribution of this genetic condition for those of Caucasian and of European descent, the rate is 1 in 500 to 700, and for individuals of Japanese descent, prevalence is only 1 in 18,500 [redacted]. Without routine screening or a well-designed prevalence study, the true prevalence of PIDD may not be well estimated.
Demographics of the target population in the indication:	PIDD can occur in adults, children and adolescents. Both male and females and all races and ethnic groups can be affected by PIDD.
Risk factors for the disease:	The only known risk factor is having a family history of a PIDD, which increases the risk of having the condition.
The main existing	Treatment will depend on the type of PIDD. Patients who suffer from

Primary immunodeficiency syndromes	
treatment options:	PIDD often receive treatment with antibiotics, steroids, immunoglobulin replacement therapy, and chemotherapy.
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	The prognosis of patients with PIDD varies depending on the etiology of the disorder, with the major factor in assessing prognosis dependent on the extent of damage to the lungs and other organs as well as how successful future complications can be prevented. Upon examining patients with a spectrum of PIDD syndromes, the European Society for Immunodeficiencies (ESID) determined infections were the most common complication, affecting 58% of patients. Among patients with PIDD the overall mortality rate was 5.2% with infection accounting for 56% of deaths in the population. For specific PIDDs the highest mortality observed were in individuals with SCID (13%) and ataxia telangiectasia (13%). Nevertheless, patient outcomes and long-term survival have improved significantly in recent years with Ig replacements therapies, improved awareness and diagnosis of PIDD, better management of infections and early access to antibiotics, advances in gene therapy, bone marrow and HSCT techniques, and enhanced intensive care services.
Important co-morbidities:	Individuals with PIDD have varied clinical presentations, and many have significant co-morbidities, most of which can be categorised as infectious or non-infectious conditions related to the immunodeficiency itself. For example, a patient with CVID may suffer from recurrent pneumonia causing irreversible lung damage (bronchiectasis) or be diagnosed with lymphoma before being identified as a patient with PIDD The frequency and the clinical impact on patients suffering with such infectious or non-infectious (i.e., autoimmunity, cancer, etc.) co-morbidities are discussed below. <u>Recurrent infections:</u> Many patients with PIDD or a secondary immunodeficiency are susceptible to persistent recurrent infections, which if left untreated, may be fatal. Various patients with PIDD report serious or chronic health conditions prior to diagnosis, primarily sinusitis (68%), bronchitis (55%), pneumonia (51%), and repeated ear infections (51%). Nearly one-third of patients also report frequent diarrhea prior to diagnosis. Although far less common, relatively high rates of malabsorption (9%), sepsis (5%), meningitis (4%), and hepatitis (3%) are also reported prior to diagnosis. It is also believed that routine vaccinations provide herd immunity to those at risk, thus decreasing the circulation of infectious diseases. <u>Non-Infections:</u> It is also known that patients with PIDD may have a predisposition to autoimmune diseases which are often triggered by dysfunction of the innate or adaptive immune response. Represented by over 80 heterogeneous conditions, autoimmune conditions are considered rare among the general population, and collectively they affect approximately 3% to 5% percent of the population in Western countries. In patients with PIDD, autoimmunity occurs at a significantly higher incidence commonly appearing as the first presentation of immune deficiency. Some of the more common autoimmune manifestations of PIDD, along with their rate of occurrence, include immune thrombocytopenia ([ITP] 34%), Evans syndrome (12%), autoimmune haemolytic anaemia (10%),

Primary immunodeficiency syndromes	
	rheumatoid arthritis (7%), anti-IgA (5%), systemic lupus erythematosus (3%), diabetes mellitus (3%), and inflammatory bowel syndrome (3%)[redacted]. Some immunodeficient patients may also have a greater risk for malignancies as a clinical complication, compared to the risk in the general population[redacted]. This susceptibility is thought to be partly associated with the patients' inability to launch an effective immune surveillance against malignant cells or agents[redacted]. Of all reported malignancies in the PIDD population, Hodgkin lymphoma and Non-Hodgkin lymphoma are the most common, accounting for 10% and 49%, respectively [redacted]. Individuals homozygous for ataxia-telangiectasia (A-T) have the highest lifetime cancer risk of 10% to 38% of all PIDD patients [redacted]. This rare neurologic PIDD, which occurs at a frequency of 1 per 40,000 to 300,000 births, is reported to account for a third of all malignancy cases observed in the PIDD population [redacted]. In a PIDD population drawn from administrative medical claims data in the US, statistically significantly higher comorbid diagnoses included chronic obstructive pulmonary disease-asthma in 51.5%, rheumatoid disease in 14%, deficiency anaemia in 11.8%, hypothyroidism in 21.2%, lymphoma in 16.7%, neurologic disorders in 9.7%, arrhythmias in 19.9%, electrolyte disorders in 23.6%, coagulopathies in 16.9%, and weight loss in 8.4% [redacted]. An analysis from the US Immunodeficiency Network Registry identified Fatigue was reported in 25.9% (95% CI 23.7–28.3) of PAD patients, compared to 6.4% (95% CI 4.9–8.2) of non-PAD. Patients with common variable immunodeficiency (CVID) had the highest prevalence of fatigue ($p < 0.001$) among all PIDD diagnoses [redacted].

Secondary Immunodeficiencies	
Incidence:	Secondary immunodeficiencies, which are more common than PIDDs [redacted] result from a variety of factors that can affect a host with an intrinsically normal immune system, including infectious agents, drugs, haematological malignancies, metabolic diseases, and environmental conditions [redacted]. SID occurs when the immune system is weakened by another treatment or illness. Hence, SIDs are not genetic in nature, but instead a result of external factors such as chronic illnesses e.g., leukaemias, chronic infections such as human immunodeficiency virus (HIV), extreme age or extreme external factors such as malnutrition, etc. Some examples of SID include the following: *Congenital acquired immune deficiency syndrome (AIDS) (with recurrent bacterial infections)* Globally, it is estimated that more than 1,000 infants are born with HIV each day [redacted]. In 2011 there were an estimated 7.6 per 100,000 population diagnosed with HIV in the EU, representing an increase of 16% of cases compared to 2004 [redacted]. *Multiple Myeloma* Worldwide, incidence ranges from 0.4 to 6 cases per 100,000 person years, representing 0.8% of all cancer diagnoses [redacted]. In 2016 an age-standardized incidence rate was estimated at 2.1/100,000 persons [redacted]. Incidence rates are highest and appear to be on the rise in North America, Australia, New Zealand, and Europe unlike rates in Asian countries which have remained considerably

Secondary Immunodeficiencies	
	stable [redacted]. *Chronic lymphocytic leukaemia (CLL) with hypogammaglobulinemia* Hypogammaglobulinemia, a common immunodeficient abnormality, develops in up to 85% of CLL patients and is highly associated with increased susceptibility to infection in all patients [redacted]. Global incidence of CLL varies, in part due to the reported differences associated with ethnicity among the population [redacted]. The estimated incidence of CLL in Europe is approximately 6.96 cases per 100 000 population annually, whereas a lower incidence of 4.5 cases per 100 000 population has been reported in the US [redacted]. *Allogeneic HSCT/with hypogammaglobulinemia* HSCT is used for a broad spectrum of indications worldwide, with a frequency that varies considerably among the world regions. In Europe allogeneic HSCTs account for 38% of all HSCT procedures [redacted]. In other regions such as Asia and the Eastern Mediterranean/Africa allogeneic HSCT are more common representing 58% and 65% of procedures.
Prevalence:	The most prevalent secondary immunodeficiency is the one caused by HIV and causes the acquired immunodeficiency syndrome, which prevalence varies worldwide. There were approximately 37 million individuals living with HIV at the end of 2020 of which 73% (~27 million) were receiving antiretroviral therapy (ART) by mid-2017 [redacted]. Some examples of SID include the following: *Congenital AIDS (with recurrent bacterial infections)* Among those with HIV in 2011, 1% of the cases (494 individuals) in the European Region were acquired by perinatal transmission[redacted]. In 2019, 0.7% of 136,449 new HIV cases occurred via mother-to-child transmission. As of 2018 10,752 persons are known to be living with perinatal HIV in the US with 1,544 children under the age of 13 diagnosed with perinatal HIV [redacted]. Of those with HIV, 26% in Europe (UK and Ireland), and 42% in the US, are estimated to have progressed to a diagnosis of AIDS [redacted]. There are numerous immunological defects in HIV infected children which cause them to be extremely vulnerable to infections, especially bacterial infections, as compared to individuals without HIV. As the disease progresses, deficits in humoral immunity are thought to be directly related to the high rate of recurrent bacterial infections in those with symptomatic HIV [redacted]. The consequences are severe infections with ubiquitous encapsulated bacteria, which appear before or with viral and other opportunistic infections. In a large observational study, the most serious bacterial infections that frequently occurred in children with perinatal HIV were bacterial sepsis (56%) and pneumonia (25%)[redacted]. *Multiple myeloma* The second most common hematologic cancer in the Western world is MM, accounting for 10% to 15% of all hematologic malignancies [redacted]. *Chronic lymphocytic leukaemia (CLL) with hypogammaglobulinemia* CLL is recognised as the most common leukaemia in the Western world accounting for approximately 30% to 40% of all forms of leukaemia [redacted]. This form of leukaemia, which primarily affects adults, results from a progressive accumulation of malignant B cells in

Secondary Immunodeficiencies	
	the marrow and blood which in many patients leads to complications of anaemia, bleeding, and susceptibility to infection [redacted]. In the EU there are approximately 46,000 individuals living with CLL according to 5-year prevalence estimates, which account for an annual prevalence of 2 cases per 100 000 population [redacted]. The highest prevalence of CLL has been reported in the Western European countries of Austria, Belgium, France, Germany, Luxembourg, and the Netherlands. Regional differences in the European population may be related to under diagnosis and in some regions misdiagnosis of CLL as Non-Hodgkin lymphoma, thereby leading to the observed variability in reported frequency rates[redacted]. *Allogeneic HSCT/with hypogammaglobulinemia* Globally transplant rates for allogeneic HSCT range from a low of 0.2 procedures per 10 million population in Vietnam, to as high as 434.9 procedures per 10 million population in Israel [redacted]. In 2017, 18,281 allogenic HSCT procedures were performed in Europe[redacted]. During allogeneic HSCT bone marrow ablation is performed in order to remove diseased marrow which is then replaced by healthy stem cells of a donor. As recipients of allogeneic HSCT undergo recovery, replaced cells require time to progressively mature into functional immune cells leaving patients relatively immunodeficient. During recovery patients who have undergone transplantation are highly susceptible to viral, bacterial and fungal infections, and may suffer a higher incidence of infections possibly related to secondary hypogammaglobulinemia [redacted]. Secondary hypogammaglobulinemia can occur in an estimated 20% to 25% of allogeneic HSCT patients within the first 100 days after transplantation[redacted].
Demographics of the target population in the indication:	SID can occur in adults, children and adolescents. Both male and females and all races and ethnic groups can be affected by SID.
Risk factors for the disease:	The specific risk factors depend on the underlying aetiology for the SID. For MM, among the general population, men are 1.5 times more likely than women to develop the disease, additionally, genetic predispositions may also increase this risk [redacted]. For example, studies conducted in Iceland and Sweden of MM have reported a more than two-fold elevated risk among those who are first degree relatives of patients with MM[redacted]. The incidence also increases with each decade of life with approximately 72% of cases occurring in patients 65 years of age or older and a median age of 70 years at diagnosis [redacted]. CLL is 30% to 50% times more common in men than women and is considered to be a disease of the aging population with incidence increasing around age 50 with a median age of approximately 70 years old at diagnosis [redacted]. HSCT patients at increased risk of developing hypogammaglobulinemia are 30 years of age or younger, male recipients of female donor cells, or have graft-versus-host disease[redacted].
The main existing treatment options:	Patients receiving immunoglobulin therapy for CLL are likely to also be receiving a number of chemotherapeutic agents, most given in combination regimens. Depending on the region, the three most frequently used agents are bendamustine, rituximab, fludarabine, and

Secondary Immunodeficiencies	
	cyclophosphamide [redacted] Chlorambucil is used in a small minority of patients. These drugs may be given in together as combination therapy and may be administered with prednisone to treat nausea and vomiting. A general side effect profile for chemotherapeutic agents is outlined earlier. For patients with chronic myelogenous leukaemia (CML), drugs known as tyrosine kinase inhibitors (TKIs) that target a specific gene found in CML are the standard treatment [redacted]. These drugs are less likely to affect normal cells, so their side effects are generally not as severe as those seen with other drugs that can be used to treat CML, such as traditional chemotherapy drugs. Besides the haematological side effects of most of TKIs like anaemia, thrombopenia and neutropenia, the most common adverse effects are oedema, nausea, hypothyroidism, vomiting and diarrhoea. More serious and possibly long-term effects include pleural effusion, prolonged QT syndrome, liver damage, and congestive heart failure. Drugs that treat HIV/AIDS known as ART are designed to slow the replication of the virus. These drugs are typically administered as a combination regimen. Examples of commonly used agents include nucleoside reverse transcriptase inhibitors (NRTIs) such as abacavir or lamivudine; non-NRTIs such as efavirenz or nevirapine; protease inhibitors like amprenavir or tipranavir; integrase inhibitors (raltegravir and dolutegravir); enfuvirtide (a fusion inhibitor) and/or entry inhibitors such as maraviroc. The most common side effects of ART are nausea, vomiting diarrhoea, rash, loss of fat particularly on the face and arms, and lipid abnormalities. Patients undergoing allogenic bone marrow transplantation will require ablative therapy with high-dose chemotherapy and/or radiation prior to transplantation. The combinations of either cyclophosphamide and busulfan or fludarabine and busulfan are 2 commonly used regimens[redacted]. Chemotherapy associated adverse reactions can range from mild/moderate such as nausea, vomiting, diarrhoea to severe such as liver/kidney damage, thrombocytopenia. Patients undergoing radiation therapy typically experience. Adverse events associated with radiation therapy are skin changes and fatigue and those that are specific to the part of the body being treated.
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	Survival studies of patients with CLL indicate a heterogeneous prognosis with a median survival of 8 to 10 years, which is likely due to 80% of patients being diagnosed prior to severe disease-progression [redacted]. This is considerably better than survival of 5 to 6 years reported in the 1970s for CLL patients [redacted]. However, bacterial infections of the respiratory tract, skin or urinary tract, remain the major cause of death in CLL patients [redacted]. Recent improvement in survival rates have also been demonstrated in individuals with MM [redacted]. Overall, 5 year age adjusted survival rates for MM patients have increased from 36% in 1998-2001 to 44% in 2006-2009[redacted]. However, younger patients have benefited from gains in survival more than older patients (75 years and older) who have poorer outcomes, which may be due to the aggressive impact of disease in the elderly compounded by their inability to receive certain intensive therapies [redacted]. Among allogeneic HSCT patients, risk of mortality has largely been associated with persistent low levels of antibody production. Transplant patients with persistent hypogammaglobulinemia, characterised by low IgG, demonstrated a 54% survival rate as compared to 71% in those with normal

Secondary Immunodeficiencies	
	levels [redacted]. Despite appropriate antimicrobial drug intervention, increased mortality in allogeneic HSCTs patients with low IgG has been associated with an increased incidence of bacterial infections [redacted]. In HIV infected children, bacterial infections are associated with increased morbidity and mortality. In particular, bacterial infections that cause pneumonia are a leading cause of illness and death in children younger than 5 years old [redacted]. Globally acute respiratory infection, which is principally caused by pneumonia, accounts for almost 2 million deaths in children younger than 5 years of age [redacted]. Mortality rates associated with pneumonia in HIV infected children are reportedly 3 to 6 times higher than rates in children with pneumonia without HIV infection [redacted].
Important co-morbidities:	Patients with a secondary immunodeficiency, which may be acquired from malignancies or HIV, are also at risk for a spectrum of infections associated with disease complications or related to the immunosuppressive impact of treatment. The risk of infectious complications, in patients with CLL early in disease, is highly associated with hypogammaglobulinemia and increased susceptibility to bacterial infections [redacted]. Recurrent infections, commonly from respiratory and severe urinary tract infections, occur in as many as 80% of patients with CLL [redacted]. Similarly, MM patients are especially prone to increased incidence of bacterial septicaemia and infection of the respiratory and urinary tracts [redacted]. In a population-based study conducted in Sweden, patients with MM were 7.1 times more likely to develop a bacterial or viral infection than the general population[redacted]. The risk of recurrent disease is also elevated in HIV infected patients [redacted] Patients with perinatal HIV frequently have occurrences of severe bacterial infections such as pneumonia (111 per 1,000 person years), bacteraemia (16 per 1,000 person years), and urinary tract infections (33 per 1,000 person years) which become more frequent with increasing immunosuppression [redacted].

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	
Incidence:	CIDP is a rare, acquired immune-mediated neuropathy primarily affecting adults characterized by progressive, symmetrical, proximal and distal weakness[redacted]. A systematic literature review and meta-analysis published in 2019 included 5 studies that estimated CIDP incidence (pooled 818 cases; 220,513,524 person-years of follow-up) [redacted]. Studies included in the estimate were rated as moderate quality. The crude meta-estimate of incidence was 0.33 (95% CI 0.21-0.53) per 100,000 person-years and ranged from 0.15 [redacted] to 1.4[redacted] per 100,000 person-years. Incidence of CIDP was higher in males versus females and ranged from 0.51 [redacted] to 0.92 [redacted] and 0.22 [redacted] to 0.48 [redacted], respectively.
Prevalence:	The estimated prevalence of CIDP in populations from the United Kingdom, Australia, Italy, Japan, and the United States is 0.8 to 8.9 per 100,000[redacted]. The Broers meta-analysis of prevalence included 9 studies for which 3,160 cases were reported among a population of 160,765,325 people [redacted]. The crude prevalence was estimated at 2.81 (95% CI 1.58-4.39) per 100,000 persons. Population prevalence estimates ranged from 0.67 [redacted] to 10.3 [redacted] per 100,000 persons. Male prevalence ranged from 1.36 [redacted] to 6.73 [redacted] per 100,000 persons. Female prevalence estimates ranged from 0.31[redacted] to 2.87 [redacted] per 100,000

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	
	persons.
Demographics of the target population in the indication:	CIDP can affect all ages but is more common in older males. It is thought that the disease is more likely to be progressive in the older age group and relapsing-remitting in younger patients [redacted].
Risk factors for the disease:	No specific predisposing factors for CIDP have been identified. There have been conflicting studies on human leukocyte antigen (HLA) type associations, but no clear genetic predisposition has been found. In several case reports, treatment with tumour necrosis factor-alpha inhibitors has been associated with the subsequent development of chronic demyelinating neuropathies[redacted]. CIDP is reported to occur more commonly in patients with diabetes mellitus (DM) but has not been rigorously tested [redacted]. A study by Said found that among 100 CIDP cases evaluated, 16% had an infectious event 6 weeks or less before CIDP onset. In an Italian CIDP cohort, Donnedu found significant associations between exposure to toxic environmental agents (odds ratio [OR] = 2.55; 95% CI, 1.42-4.55), cigarette smoke (OR = 2.02; 95% CI, 1.4-2.93), and dietary supplements (OR = 1.97; 95% CI, 1.08-3.58) and development of CIDP [redacted].
The main existing treatment options:	Treatment options are described by "The European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision [redacted]." 1) **Corticosteroids:** Strongly recommended as first-line therapy although the best corticosteroid regimen is unknown. Pulsed high-dose corticosteroid treatment with oral dexamethasone or IV methylprednisolone may be an alternative to daily prednisone/prednisolone or dexamethasone, or both. Long-term treatment may induce significant side-effects. Treatment with IVIg may be considered first-line for patients with motor CIDP. 2) **IVIg:** Strongly recommended for first-line therapy. Evidence of IVIg benefit has been demonstrated in multiple placebo-controlled trials. No preference for IVIg over corticosteroids. 3) **SCIg:** Strongly recommended for maintenance therapy of CIDP. No preference for IVIg or SCIg for maintenance therapy. 4) **Plasma exchange:** Strongly recommended. Initial treatment with 5 exchanges over 2 weeks; thereafter individually adapted. Peripheral veins should be used, if possible. 5) **Immunosuppressive drugs:** The guideline advised to use immunosuppressive drugs azathioprine, cyclophosphamide, ciclosporin, mycophenolate mofetil, and rituximab after failure with recommended treatments or as add-on medication. The guideline strongly recommends against treatment with interferon beta-1a. The guideline weakly recommends against treatment with methotrexate and fingolimod. The guideline advises against use of alemtuzumab, bortezomib, etanercept, fampridine, fludarabine, immunoadsorption, interferon alpha, abatacept, matalizumab, and tacrolimus. Not included in the guidelines is efgartigimod aiming to reduce

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)	
	pathogenic antibody levels through anti- neonatal crystallizable fragment receptor (FcRn) action.
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	In a population-based study from Iceland with 21 years of follow-up, Hafsteinssdottir identified 19 individuals with incident or prevalent CIDP. The cohort was primarily male (14/19) with mean age at diagnosis 57 years (range 19-81) with women diagnosed at an earlier age (mean age 36 years) than men (mean age 63 years). Mean follow-up was 6.9 years. Risk for mortality was similar to the underlying Icelandic population (standardized mortality ratio 0.9, 95% CI 0.3-2.2) [redacted].
Important co-morbidities:	A study by Donnedu evaluated comorbidities associated with CIDP in 393 patients in Italy based on a structured web-based questionnaire. All patients included in the evaluation met European Federation of Neurological Societies and Peripheral Nerve Society criteria and included in an Italian CIDP database. One or more comorbidities were reported in 294 (75%) of the CIDP cohort. Diabetes (14%), monoclonal gammopathy of undetermined significance (MGUS) (12%) and other immune disorders (16%) were more frequent in the CIDP cohort than would be expected based on rates estimated from the general European population. CIDP patients with diabetes had more disability and reported lower quality of life than those without diabetes. Patients with MGUS tended to be older at symptom onset and experienced more frequent motor CIDP [redacted].

Part II: Module SII - Non-clinical part of the safety specification

The below provides an overview of the studies involved in the non-clinical study program for HyQvia. For ease of reading, study tables have been organised by test article(s):

- Studies with IG 10% (KIOVIG/GAMMAGARD LIQUID)
- Studies with rHuPH20
- Studies with IG 10% and rHuPH20
- Four local tolerance studies have been conducted with Immune Globulin Subcutaneous (IGSC) 10% and rHuPH20 in combination.

Key safety findings from non-clinical studies and relevance to human usage:

Study		**Relevance for Human Usage**
Test Article: IG 10%		
Single dose toxicity	PV0330101 Determination of Acute Toxicity in Mice after Intravenous Administration of Immune Globulin Intravenous (Human) 10% Triple Virally Reduced (TVR) Solution.	Mice were administered a single dose of 2,500, 5,000, or 10,000 mg/kg IGI, 10% or GAMMAGARD S/D, the highest applicable volume, by the IV route. Behavioural depression with or without dyspnoea was observed in the surviving animals of the group treated with 10,000 mg/kg IGI, 10%. No treatment-related histopathological changes were observed in the lung, heart, or kidneys up to this dose. The no observed adverse effect level (NOAEL) for this study in mice was 5,000 mg/kg for IGI, 10%.
	PV0340101 Determination of Acute Toxicity in Rats after Intravenous Administration of Immune Globulin Intravenous ([IGIV] Human) 10% TVR Solution.	Rats were administered a single dose of 2,000 mg/kg IGI, 10% or GAMMAGARD S/D by the IV route (PV0340101). No treatment-related findings were revealed by gross necropsy. The NOAEL was 2,000 mg/kg for IGI, 10%.
Repeat-dose toxicity	None	-
Reproductive/Developmental toxicity	None	-
Genotoxicity	OEFZS-UL-0159 Salmonella typhimurium Reverse Mutation Test	There was no statistically significant increase in the mutation frequency. Metabolic activation did not change these results. IGI, 10% is not considered to have genotoxic potential.
Carcinogenicity	None	-
Local tolerance	PV0350101 Investigation on Local Tolerance of IGIV (Human) 10% TVR Solution in Rabbits.	Excellently tolerated after IV infusion, slight irritation after intra-arterial or paravenous administration. The observed irritation and inflammatory reactions in studies in rabbits for other routes are considered to be a consequence of the animals' immune response

Study		Relevance for Human Usage
		to the human IgG preparation and considered of limited relevance for human usage.
Test Article: rHuPH20		
Single dose toxicity	03-007/R03005 A Preliminary IV Toxicity Study in Rats with Optiphase™	Sprague-Dawley rats were administered a single dose of 10,500 U/kg rHuPH20 by IV route and 2 additional rats received only a vehicle formulation. Histological analysis revealed slight renal tubule dilation with the lumina containing an amorphous material consistent with hyaline casts in all 5 male rats. All other tissues evaluated male rats and all tissues in the female rats were within normal limits.
Repeat-dose toxicity	RDH00007/R05015 Recombinant Human Hyaluronidase: Pilot Ascending Dose Peribulbar and Subcutaneous Tolerability Study in Rhesus Monkeys	The SC no effect level was considered to be at least 45,000 U per injection.
	RDH00006/R05014 A Single/Repeat-Dose Toxicity Study of Hyaluronidase Administered by Peribulbar and Subcutaneous Injection to Rhesus Monkeys, with a 3-Week Recovery	rHuPH20 was well tolerated by male and female rhesus monkeys when administered as single peribulbar injections in one or both eyes and single or repeat once weekly SC injections (up to 2 weeks) at 130, 3,880, and 38,800 U/injection. Under the conditions of the study, a NOAEL of 38,800 U/injection (12,000 U/kg) was determined for rHuPH20 treatment by either peribulbar or SC routes of administration. Within the limits of detection, neutralizing antibodies were not identified.
	1005-1253/R05108 PH20: A 6-Week Toxicity Study Following Repeated Intravesical Administration to Cynomolgus Monkeys.	A six-week toxicity study to establish the toxicity of rHuPH20 in cynomolgus monkeys when administered by intravesical route (urinary bladder) once weekly for 6 consecutive weeks followed by a seven-day observation period was conducted. There was no mortality subsequent to treatment. Clinical observations included swelling of the skin, skin red in colour, or red spots on the urogenital area, penis/vulva, and sacrum. These clinical signs were noted both in control and rHuPH20 treated animals and were considered procedure-related from the catheterisation. In addition, one episode of vomiting was observed in one rHuPH20 and one observation of decreased activity and lying on cage floor was noted in one rHuPH20 treated female. Due to the single-episode occurrence of these clinical observations, they could not be clearly attributed to rHuPH20 treatment. No treatment- related macroscopic or microscopic observations were noted in any of the tissues examined. Toxicokinetic (TK) evaluation

Study		Relevance for Human Usage
		performed from plasma bioanalysis of hyaluronidase activity noted no detectable levels among any of the plasma samples. In conclusion, the weekly intravesical administration of rHuPH20 for 6 consecutive weeks to cynomolgus monkeys at dose levels of 0 or 200,000 U/ injection (77,000 U/kg) was not associated with any overt toxicity.
	SNBL.258.04/R08056 A 7-Day Repeat-Dose Intravenous and Subcutaneous Toxicity Study of rHuPH20 in Cynomolgus Monkeys.	Administration of rHuPH20 was well tolerated by cynomolgus monkeys via either IV or SC delivery at a dose of 5 mg/kg (580,000 U/kg) once daily for 7 consecutive days. The NOAEL was 5 mg/kg (580,000 U/kg) by either SC or IV routes of administration.
	SNBL.258.01/R09050 A 39-Week Toxicity Study of rHuPH20 Administered Subcutaneously in Cynomolgus Monkeys with a Recovery Phase.	Treatment-related minimal SC perivascular lymphoplasmacytic infiltration present at injection site in all animals administered 2.0 mg/kg rHuPH20 and in 1/4 males and 1/4 females administered 0.2 mg/kg rHuPH20. At the end of recovery period, minimal SC perivascular lymphoplasmacytic infiltration present in a single male that had been administered 2.0 mg/kg rHuPH20 indicating substantial recovery, and therefore recoverability. Plasma hyaluronidase activity increased from study day 1 to 85 followed by a decrease on days 183 and 267. Loss of hyaluronidase activity following chronic repeated doses of 2.0 mg/kg consistent with development of hyaluronidase neutralising activity in plasma specimens. The NOAEL for rHuPH20 was 2.0 mg/kg (240,000 U/kg), the highest dose level administered. The SC NOAEL (2 mg/kg; 240,000 U/kg) exceeds the expected dose level of rHuPH20 in humans by a factor of approximately 3200-fold. Because of body surface area (factor 3.1), the human equivalent dose is 0.65 mg/kg which represents a safety margin at least 1,032-fold. These results support the use of rHuPH20 as a locally acting, transiently active, permeation enhancer for SC administration of IG, 10%.
Reproductive/Developmental toxicity.	RDH00016/R07046 Subcutaneous Dosage-Range Developmental Toxicity Study of rHuPH20 in Mice.	Daily SC administration of 10 and 30 mg/kg rHuPH20 was found to be toxic to developing embryos/foetuses as determined by increased % resorptions and litter size with no effects on maternal BW or BW gain at doses as high as 10 mg/kg. Based on the results of this study it can be speculated that the total litter losses observed at SC dose of 30 mg/kg/day and reduced litters at 10 mg/kg were the result of the

Study		Relevance for Human Usage
		disruption or degradation of hyaluronic acid in the developing embryo by rHuPH20. Lower doses (1 and 3 mg/kg/day) did not result in maternal toxicity and did not appear to affect embryo development.
	RDH00017/R08176 Subcutaneous Developmental Toxicity Study of rHuPH20 in Mice.	No clear maternal toxicity (clinical observations, BW gains) occurred at any of the doses tested up to 18 mg/kg/day. Therefore, the NOAEL for maternal toxicity was 18 mg/kg/day. Reductions in foetal weight and increases in the number of late resorptions were observed in the 9 and 18 mg/kg dosage groups. There were no other adverse effects (no malformations or variations) on embryo-foetal development. NOAEL for embryo-foetal development was 3.0 mg/kg. TK analysis of plasma hyaluronidase activity generally confirmed dose-dependent increases in exposure to rHuPH20 after SC administration in the dams. Retrospective analysis of a subset of TKs samples collected for the study on day 15 of gestation demonstrated that all dams tested developed anti-rHuPH20 antibodies within comparable ranges across all 3 dose groups. These anti-rHuPH20 antibodies were also shown to be predominately of the IgG isotype. Because IgG antibodies are known to cross the placenta during gestation [redacted], the foetuses were likely exposed to the maternal anti-rHuPH20 antibodies. Since antibody titre ranges were similar across all rHuPH20 dosed groups and anti-rHuPH20 titres did not correlate with the dose-dependent observation of resorptions at ≥9 mg/kg/day, these data suggest that anti-rHuPH20 antibodies had no effects on embryo-foetal development in the CD-1 mouse model.
	RDH00019/R09058 Subcutaneous Developmental and Perinatal/ Postnatal Reproduction Toxicity Study of rHuPH20 in Mice, Including a Postnatal Behavioral/ Functional Evaluation.	The maternal NOAEL for rHuPH20 was 9 mg/kg/day. No effects on viability and growth in the offspring including sexual maturation, learning, memory, and the ability to produce an F2 generation. The NOAEL for maternal reproduction and offspring development was also 9 mg/kg/day.
Pre/Postnatal Development.	20029369/12096 Evaluation of Anti-rHuPH20 Antibodies Following Administration of rHuPH20 by Subcutaneous Injection in Mice (Developmental and Perinatal/Postnatal Reproduction	Alignment of the timelines for plasma sample analysis of anti- rHuPH20 antibodies in this study and the assessments of neurological and reproductive system developmental milestones in study RDH00019, demonstrates that exposure of offspring to anti-rHuPH20 antibodies throughout all stages of

Study		Relevance for Human Usage
	Study Design).	development from late gestation through adulthood does not result in adverse effects on overall growth, neurological development, sexual maturation, reproductive function or mating outcome in offspring of rHuPH20 treated mice.
Juvenile Toxicity	20039195/13123 A 6-week Subcutaneous Dose-Range Finding Toxicity Study of rHuPH20 in Juvenile Mice	Juvenile mice were administered rHuPH20 SC either daily at 1, 3 or 9 mg/kg/day or weekly at 3 or 9 mg/kg/week from postnatal day (PND) 7 to PND 42. SC administration of rHuPH20 either daily or once weekly was well tolerated in juvenile mice at levels up to 9.0 mg/kg/dose. There were no adverse effects observed at doses up to 9.0 mg/kg/dose. Anti-rHuPH20 antibodies were detected in all rHuPH20-dosed groups by PND 30 and were cross-reactive to rMuPH20 and rMuHyal5, thus supporting the relevance of the CD-1 mouse model for studying the potential impact of anti-rHuPH20 antibodies.
	13125 Tolerability Study of Daily Subcutaneous Administration of rHuPH20 in Juvenile Mice	Juvenile mice were administered daily SC injections of rHuPH20 at 0 mg/kg/dose (control), 3 mg/kg/dose or 9 mg/kg/dose from PND 7 to PND 90. No adverse effects were noted in any dosed groups as a result of rHuPH20 administration, and no marked differences in average BWs were observed across groups.
	20081082 Good laboratory practices toxicity study to determine the potential toxicity of rHuPH20 as well as de novo produced anti-rHuPH20 antibodies	rHuPH20 was administered SC to juvenile mice daily from PND 7 to PND 30 and thereafter administered weekly until PND 129 (after reproductive assessments for the juvenile subset) or PND 241 (chronic subset). Evaluations included neurobehavioral assessments, reproductive capacity and foetal evaluations, and chronic toxicity through adulthood. Subcutaneous administration of rHuPH20 in male and female Crl:CD1(ICR) mice at a dose of 1 mg/kg/dose did not lead to treatment-related mortality or clinical signs and there were no rHuPH20-related effects on BWs or BW gains. There were no rHuPH20-related effects on sexual maturation, neurobehavioral endpoints or reproductive parameters (mating and fertility, sperm motility, concentration or morphology, ovarian, uterine, or litter observations) in animals assigned to the juvenile subset, and rHuPH20 did not produce any foetal external, visceral, or skeletal abnormalities. In addition, there were no rHuPH20-related effects on any ophthalmological or clinical pathology parameters evaluated in mice assigned to the

Study		Relevance for Human Usage
		chronic subset. There were observations of increased splenic weights with an associated increase in haematopoiesis in females assigned to the chronic subset at 1 mg/kg/dose rHuPH20. However, these findings were considered unrelated to rHuPH20 because it was most likely to be a secondary/reactive response to the inflammation at the site of rHuPH20 administration. Minimal to moderate, non-adverse microscopic findings attributed to rHuPH20 were limited to injection site reactions (primarily a mixed cell infiltration within the SC tissues with occasional observations of SC mixed cellular inflammation) noted in male and female mice in the chronic subset. All animals administered rHuPH20 generated anti-rHuPH20 antibodies with a high incidence of rHuPH20 neutralising activity and cross-reactivity to both the rMuPH20 and rMuHyal5 sperm hyaluronidases. This confirms the relevance of the study to assess the safety of both rHuPH20 and de novo produced anti-rHuPH20 antibodies.
Genotoxicity	None	-
Carcinogenicity	None	-
Local Tolerance	04-007/R05049 A Preliminary IP Local Tolerance Study in Rats with HUA0415C	Sprague-Dawley female rats were dosed with either control saline or rHuPH20 and analysed for necropsy both at short-term (7 days) and at long-term (28 days). Cytologic changes in epithelium of distal convoluted tubules in all 3 long-term animals at highest dose (15,000 U/kg) and one animal at intermediate dose (1,500 U/kg). Hydrometra in all long-term animals with renal tubule changes, and also in 2 short-term animals from highest dose. Based on the observed hydrometra and distal renal tubule changes, the NOAEL for rHuPH20 in this study was determined to be below the dose of 15,000 U/kg. Thus, the dose of 1,500 U/kg was considered the maximum tolerated dose in this study.
Other Toxicity Studies.	12124 Antibody Response Against rHuPH20 in New Zealand White (NZW) Rabbits Following Three Separate Immunization Procedures.	The results support the use of either a daily or weekly SC dosing regimen for the generation of high-titre, sustained levels of anti-rHuPH20 antibodies in female NZW rabbits. The results also demonstrate that anti-rHuPH20 antibodies can bind in vitro to the recombinant form of rabbit PH20, and that the incidence of cross-reactivity is high (>80%) supporting the use of the NZW rabbit model to study the potential

Study		Relevance for Human Usage
		impact of anti-rHuPH20 antibodies.
	20035646/12208 Effects of Anti-rHuPH20 Antibodies on Male Fertility and General Reproduction in the New Zealand White Rabbit.	All rHuPH20-treated males generated persistent anti-rHuPH20 antibody titres prior to/during mating and titres were maintained during semen evaluations and assessments of mating outcome. Anti-rHuPH20 antibodies cross-reacted with recombinant rabbit PH20, supporting the relevance of the NZW rabbit model for evaluating the potential effects of anti-rHuPH20 antibodies on male fertility. The anti-rHuPH20 antibodies in rabbit plasma also demonstrated neutralising activity and cross-neutralising to rRbPH20. Reactivity of rabbit IgG to the rabbit PH20 and the neutralisation of rabbit PH20 hyaluronidase activity demonstrates the relevance of the NZW rabbit model for evaluating the potential effects of anti-rHuPH20 antibodies on male fertility to rHuPH20. In the absence of any biologically meaningful effects on sperm parameters or Caesarean-section evaluations in the mated females (mating outcomes), it is concluded that persistent exposure to anti-rHuPH20 antibodies prior to mating had no effect on male reproductive functions, mating behaviour or fertility.
	20035449/12195 Effects of Anti-rHuPH20 Antibodies on Female Fertility and Embryo- Foetal Development with Postnatal Assessments in the New Zealand White Rabbit.	Maternal exposure to elevated titres of anti-rHuPH20 antibodies prior to mating and throughout gestation had no effect on mating and fertility. Maternal anti-rHuPH20 antibodies transferred to their offspring during gestation, persisted through at least 3 months of age and had no effect on embryo-foetal or postnatal development of offspring including developmental milestones, growth, behaviour, maturation or offspring mating and fertility.
Test Articles: IGSC 10% and rHuPH20		
Local Tolerance	AU0206W01 Pre-Clinical Studies on the Subcutaneous Application of GAMMAGARD LIQUID after HYLENEX Pre-treatment: Local Tolerance in the Rabbit.	Mild to moderate SC inflammatory reactions were observed after single or repeated application of IG 10% with and without rHuPH20. These results were considered a consequence of the rabbit's immune response against the human IgG preparation and considered of limited relevance for human usage.
	R09131 Local Tolerance Feasibility Study after Repeated Subcutaneous (Bolus) Administration of GAMMAGARD 10% with	No test-item-related adverse effect after repeated SC administration of IG 10% with and without rHuPH20. IG 10% with and without rHuPH20 are considered well tolerated.

Study		Relevance for Human Usage
	rHuPH20 in SCID[1] Mice.	
	11018 Assessment of Induration Following Subcutaneous Infusions of Immunoglobulin in Yucatan Micro-Pigs	It was demonstrated that pre-administration of rHuPH20 increases dispersion of IgG, significantly reduces in-line pressure, and mitigates infusion site induration with administration of large volumes of IgG in a porcine model.
	11028 Evaluation of Induration via Laser Doppler Assessment of Blood Flow Following Subcutaneous Infusions of Immunoglobulin in Yucatan Micro- Pigs	It was demonstrated that pre-administration of rHuPH20 increases dispersion of IgG, significantly reduces in-line pressure, and mitigates infusion site induration with administration of large volumes of IG 10% in a porcine model. Local cutaneous blood perfusion is improved in the presence of rHuPH20 during large volume infusions of IG 10%.

[1] SHO- PrkdcscidHrhr mice, commonly referred to as SCID

Part II: Module SIII - Clinical trial exposure

Table SIII.1: Clinical study duration of exposure by indication (All HyQvia treated subjects)

Indication: Cumulative		
Duration of exposure	**Persons**	**Person time (years)**
0 to <0.5 years	67	15.85
0.5 to <1 year	24	15.27
1 to <2 years	111	149.85
2 to <3 years	41	107.36
3 or more years	71	275.03
Total	**314**	**563.34**

Indication: Cumulative - Studies 160602, 160603, 160902, 161101, 161503, 161504, 161403, 161505.

Indication-PID		
Duration of exposure	**Persons**	**Person time (years)**
0 to <0.5 years	51	12.46
0.5 to <1 year	13	9.02
1 to <2 years	94	123.99
2 to <3 years	21	58.95
3 or more years	31	101.95
Total	**210**	**306.37**

PID = Primary immune deficiency.
Indication: PID - Studies 160602, 160603, 160902, 161101, 161503, 161504.

Indication-CIDP		
Duration of exposure	**Persons**	**Person time (years)**
0 to <0.5 years	16	3.39
0.5 to <1 year	11	6.25
1 to <2 years	17	25.85
2 to <3 years	20	48.41
3 or more years	40	173.08
Total	**104**	**256.98**

CIDP = Chronic inflammatory demyelinating polyradiculoneuropathy.
Indication: CIDP - Studies 161403, 161505.

[redacted]

Table SIII.2: Clinical study exposure by age group and gender by indication (All HyQvia treated subjects)

Indication: Cumulative						
Age group	**Persons**			**Person time (years)**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<18 years	84	38	122	108.74	48.51	157.26
18 to <65 years	69	87	156	161.68	168.80	330.48
65 to <75 years	18	10	28	39.83	22.25	62.08
75 or more years	6	2	8	6.28	7.26	13.53
Total	**177**	**137**	**314**	**316.53**	**246.81**	**563.34**

Indication: Cumulative - Studies 160602, 160603, 160902, 161101, 161503, 161504, 161403, 161505

Indication-PID						
Age group	**Persons**			**Person time (years)**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<18 years	84	38	122	108.74	48.51	157.26
18 to <65 years	31	45	76	63.95	64.03	127.98
65 to <75 years	3	8	11	4.44	12.90	17.34
75 or more years	0	1	1	0.00	3.79	3.79
Total	**118**	**92**	**210**	**177.13**	**129.23**	**306.37**

PID = Primary immune deficiency.
Indication: PID - Studies 160602, 160603, 160902, 161101, 161503, 161504.

Indication-CIDP						
Age group	**Persons**			**Person time (years)**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<18 years	0	0	0	0.00	0.00	0.00
18 to <65 years	38	42	80	97.73	104.77	202.50
65 to <75 years	15	2	17	35.39	9.35	44.74
75 or more years	6	1	7	6.28	3.46	9.74
Total	**59**	**45**	**104**	**139.40**	**117.58**	**256.98**

CIDP = Chronic inflammatory demyelinating polyradiculoneuropathy.
Indication: CIDP - Studies 161403, 161505.

[redacted]

Table SIII.3: Clinical study exposure by ethnic origin by indication (All HyQvia treated subjects)

Indication: Cumulative		
Ethnic origin	**Persons**	**Person time (years)**
American Indian or Alaska Native	2	7.38
Asian	3	4.39
Black or African American	4	10.25
White/Caucasian	296	523.47
Multiple	4	9.33
Other	1	1.27
Not Reported	4	7.25
Total	**314**	**563.34**

Indication: Cumulative - Studies 160602, 160603, 160902, 161101, 161503, 161504, 161403, 161505.

Indication- PID		
Ethnic origin	**Persons**	**Person time (years)**
American Indian or Alaska Native	1	3.10
Asian	3	4.39
Black or African American	4	10.25
White/Caucasian	197	280.64
Multiple	3	5.58
Other	1	1.27
Not Reported	1	1.13
Total	**210**	**306.37**

PID = Primary immune deficiency.
Indication: PID - Studies 160602, 160603, 160902, 161101, 161503, 161504.

Indication- CIDP		
Ethnic origin	**Persons**	**Person time (years)**
American Indian or Alaska Native	1	4.27
Asian	0	0.00
Black or African American	0	0.00
White/Caucasian	99	242.84
Multiple	1	3.75
Other	0	0.00
Not Reported	3	6.12
Total	**104**	**256.98**

[redacted]

CIDP = Chronic inflammatory demyelinating polyradiculoneuropathy.
Indication: CIDP - Studies 161403, 161505.

Table SIII.4: Clinical study infusion by indication (All HyQvia treated subjects)

Indication-Cumulative	
Infusion category	**Persons**
Subjects who received <10 infusions	75
Subjects who received 10 to 30 infusions	132
Subjects who received 31 to 60 infusions	70
Subjects who received >60 infusions	37
Total	**314**

Indication: Cumulative – Studies 160602, 160603, 160902, 161101, 161503, 161504, 161403, 161505.

Indication-PID	
Infusion category	**Persons**
Subjects who received <10 infusions	56
Subjects who received 10 to 30 infusions	103
Subjects who received 31 to 60 infusions	40
Subjects who received >60 infusions	11
Total	**210**

PID = Primary immune deficiency.
Indication: PID - Studies 160602, 160603, 160902, 161101, 161503, 161504.

Indication-CIDP	
Infusion category	**Persons**
Subjects who received <10 infusions	19
Subjects who received 10 to 30 infusions	29
Subjects who received 31 to 60 infusions	30
Subjects who received >60 infusions	26
Total	**104**

CIDP = Chronic inflammatory demyelinating polyradiculoneuropathy.
Indication: CIDP - Studies 161403, 161505.

[redacted]

Part II: Module SIV - Populations not studied in clinical trials

SIV.1. Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
Subjects with a history of known allergy, hypersensitivity, or persistent reactions (urticaria, breathing difficulty, severe hypotension, or anaphylaxis) following IGIV, IGSC, immune serum globulin (ISG), albumin infusions, or hyaluronidase of human or animal (including bee or vespid venom) origin	To prevent serious anaphylactic reactions.	No	As with any product, hypersensitivity reactions are possible. Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency is an important identified risk with the product. The use of HyQvia is contraindicated in patients with known hypersensitivity to human immunoglobulins, systemic hypersensitivity to hyaluronidase or recombinant hyaluronidase, or hypersensitivity to any of the excipients used in the manufacture of the product.
Subjects with IgA deficiency and known anti-IgA antibodies	To prevent serious anaphylaxis reactions	No	Administering an IgA containing product in patients with selective IgA deficiency with antibodies against IgA can result in anaphylaxis. The use of HyQvia is contraindicated in patients who suffer from IgA deficiency with antibodies against IgA.
Subjects positive at enrollment for one or more of the following: HBsAg, polymerase chain reaction (PCR) for hepatitis C virus (HCV), PCR for HIV Type 1/2	Transmission of infectious agents such as hepatitis B virus (HBV), HCV, and HIV is a theoretical possibility with any blood- or plasma-derived medicinal product. Positive test results prior to study entry would preclude the ability to determine whether any such infection or positive antibody test is the result of administration of the investigational product.	No	In certain cases, the benefits of IG therapy may outweigh the risk of transmission of an infectious agent. Physicians must perform a baseline assessment of all risk factors and weigh the benefit-risk balance for each individual prior to prescribing therapy. Additionally, HIV/HBV/HCV patients may require IgG therapy in certain clinical situations.
Subjects with levels of alanine	Since IV IgG has been associated with	No	Having an elevated transaminase per se is not a contraindication. It

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times the upper limit of normal (ULN) for the testing laboratory	elevated transaminases in the past (mostly due to HCV), such subjects are not allowed in studies to avoid that any such changes could be attributed to the product in error.		does not impact the efficacy of the IgG and treatment of patients with elevated transaminases with IV or SC IgG and does not present a safety risk to the patient.
Subjects with neutropenia (defined as an absolute neutrophil count ≤500/mm^3)	Severe neutropenia increases the risk of serious infections, such as sepsis, even in subjects with normal immunoglobulins. Treatment with IV IgG may appear ineffective in such subjects with PID; thus, they are excluded from clinical trials.	No	Physicians must perform a baseline assessment of all underlying risk factors and weigh the benefit-risk balance for each individual prior to prescribing therapy. Patients with antibody deficiency require antibody replacement even if they have additional risk factors, such as neutropenia or T cell abnormalities.
Subjects with a history of thrombophilia or thrombotic episodes (e.g., deep vein thrombosis, myocardial infarction [MI], cerebrovascular accident, pulmonary edema, or sickle cell anaemia with history of painful vaso-occlusive crisis)	Thromboembolic events are a known risk of IV immunoglobulin treatment. The risk of thrombosis by a new product cannot be justified until the efficacy of the product has been demonstrated.	No	In certain cases, the benefits of immunoglobulin therapy may outweigh the risk of a thrombotic event. Physicians must perform a baseline assessment of all risk factors and weigh the benefit-risk balance for each individual prior to prescribing therapy.
Subjects with bleeding disorders or who were receiving anticoagulation therapy at the time of study enrollment	Concurrent anticoagulant therapy would preclude the ability to accurately monitor for the occurrence of thrombotic events related to immunoglobulin treatment. Further, the risk of hematoma from SC infusions may increase in patients who are anti-coagulated.	No	In certain cases, the benefits of immunoglobulin therapy may outweigh the risk of a thrombotic event. Physicians must perform a baseline assessment of all risk factors and weigh the benefit-risk balance for each individual prior to prescribing therapy. SC infusions might be undesirable in patients with significant anticoagulation.

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
Subjects with abnormal protein loss (e.g., protein losing enteropathy, nephrotic syndrome, or severe lung disease)	It is impossible to do proper PK assessments in subjects with abnormal protein loss, so these subjects are excluded from clinical studies. Subjects who only have abnormal losses and not PIDD should not be treated with immunoglobulin and are not candidates for the study. In general, immunoglobulin replacement therapy is considered futile in conditions such as protein losing enteropathy, nephrotic syndrome, and severe lung disease. Correction of the underlying disorder usually results in normalisation of insufficient immunoglobulin levels caused by these conditions.	No	Physicians must perform a baseline assessment of all underlying diseases and weigh the benefit-risk balance for each individual prior to prescribing therapy. PIDD patients who also have abnormal protein loss are properly treated with replacement therapy while simultaneously addressing the cause of the abnormal losses.
Subjects with myeloma or current history of any malignancy (other than adequately treated basal cell or squamous cell carcinoma of the skin or carcinoma in situ of the cervix) and subjects treated with immunosuppressive chemotherapeutic agents during the study period	Myeloma/other malignancies and immunosuppressive chemotherapeutic therapies would alter a subject's host defences beyond antibody deficiency and make it impossible to assess the effectiveness of the immunoglobulin.	No	-
Subjects who had been exposed to any blood product other than an IGIV, SC immunoglobulin, ISG preparations, or	There are certain risks common to administration of any blood- or plasma-derived medicinal product; notably,	No	The product labelling provides awareness to the prescribing physicians regarding the precautions for use of blood- and plasma-derived medicinal products. Physicians must weigh

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
albumin within the 6 months prior to study entry	transfer of infectious agents, renal complications, hemolysis, or thrombosis. These may not be apparent for several months. Although this is true for IgG products as well, these patients cannot stop their underlying treatment for any length of time.		the benefit-risk balance for each individual prior to prescribing.
Subjects who received antibiotic therapy for the treatment of infection within 7 days prior to enrollment or who were receiving prophylactic antibiotic therapy at the time of enrollment which could not be stopped	A key endpoint in the HyQvia clinical study program was to determine the efficacy of the active ingredient in reducing rates of infection. Concurrent antibiotic therapy would affect the ability to accurately assess the effect of HyQvia therapy on infection rates.	No	Physicians must perform a baseline assessment of all underlying risk factors and concurrent medicinal therapies and weigh the benefit-risk balance for each individual prior to prescribing therapy. The use of antibiotics in patients receiving HyQvia does not present a safety concern.
Subjects who had participated in another clinical study involving an investigational product or device within 28 days prior to study entry	Subjects with recent participation in other clinical studies involving investigational products or devices are typically excluded from clinical trials in order to accurately assess subject responses to the investigational product.	No	Physicians must perform a baseline assessment of all underlying risk factors and weigh the benefit-risk balance for each individual prior to prescribing therapy.
Females who were pregnant or lactating at the time of study enrollment	Pregnant and lactating females are typically excluded from clinical trials for safety and ethical reasons.	Yes	-
Subjects with serum creatinine levels greater than 1.5 times the ULN for age and gender Subjects who had creatinine clearance (CLcr)	IGIV therapy has been associated with rare cases of renal dysfunction/renal failure and increases in serum creatinine levels. Inclusion of	No	-

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
values, calculated according to the formula below, which were <60% of normal for age and gender: for males: CLcr = [(140 – age (years)) * (BW (kg))/[72 * (serum creatinine (mg/dL)]; for females: CLcr = [(140 – age (years)) * (BW (kg)) *0.85] / [72 * (serum creatinine (mg/dL))]	subjects with increased serum creatinine levels or decreased CLcr values would affect the ability to monitor for true cases of investigational treatment-related renal dysfunction/renal failure. The risk of exacerbating renal dysfunction cannot be justified until the efficacy has been demonstrated.		
Subjects with a total protein level >9 g/dL and subjects with macroglobulinemia (IgM) or paraproteinemia	Elevated protein levels can increase serum viscosity and thereby increase the risk of thrombotic complications. These risks cannot be justified until the efficacy of the product has been demonstrated and a proper risk/benefit analysis can be provided.	No	Physicians must perform a baseline assessment of all underlying risk factors and weigh the benefit-risk balance for each individual prior to prescribing therapy.
Subjects with anaemia that in the opinion of the investigator precluded phlebotomy for laboratory studies	The ability to obtain sufficient samples for laboratory testing is important in order to obtain accurate and consistent serological assessments across the entire trial population. The risk of exacerbating anaemia is not justified in a clinical study where there is not a direct benefit to the subject.	No	Physicians must perform a baseline assessment of all underlying risk factors and weigh the benefit-risk balance for each individual prior to prescribing therapy. In a clinical setting, blood samples are obtained for the benefit of the patient, not for the clinical study.
Subjects with severe dermatitis or anatomical abnormality on one or both thighs that would have precluded adequate sites for	Medical or anatomical obstructions to selected product administration sites would affect the ability to ensure consistency of product	No	Physicians must perform a baseline assessment of all underlying risk factors and weigh the benefit-risk balance for each individual prior to prescribing therapy.

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
safe product administration	administration across the entire trial population.		
Subjects positive at enrollment for one or more of the following: HBsAg, PCR for HCV, PCR for HIV Type 1/2	Transmission of infectious agents such as HBV, HCV, and HIV are a theoretical possibility with any blood- or plasma-derived medicinal product. Positive test results prior to study entry would preclude the ability to determine whether any such infection or positive antibody test is the result of administration of the investigational product.	No	In certain cases, the benefits of immunoglobulin therapy may outweigh the risk of transmission of an infectious agent. Physicians must perform a baseline assessment of all risk factors and weigh the benefit-risk balance for each individual prior to prescribing therapy. Additionally, HIV/HBV/HCV patients may require IgG therapy in certain clinical situations.

SIV.2. Limitations to detect adverse reactions in clinical trial development programmes

Ability to Detect Adverse Reactions (AR)	Limitation of Trial Program	Discussion of Implications for Target Population
Which are Rare	A total of 314 subjects have been exposed to HyQvia in clinical trials: 122 subjects less than 18 years of age, 156 subjects between the ages of 18 and 65 years, and 36 subjects of age 65 years and over.	Due to the small clinical trial population, and small number of participants at the extremes of young and old age, ARs which occur with frequencies <1/314 or which are age-related may not be adequately reflected in clinical trial results. However, across all clinical trials, the rate of total adverse drug reactions (ADRs) per infusion obtained for IGSC 10% with rHuPH20 is consistent with published data on SC administered IgG [redacted].
Due to Prolonged exposure	In clinical trials, 111 subjects have been exposed to HyQvia for a period of 1 to <2 years, 41 subjects for a period of 2 to <3 years, and 71 subjects for a period of 3 or more years.	No safety concerns have been observed in clinical trials which are attributed to prolonged exposure to HyQvia. No significant amount of safety data beyond 3 years is currently available; however, long-term data was collected during the post-authorisation safety studies (PASS) 160602,

Ability to Detect Adverse Reactions (AR)	Limitation of Trial Program	Discussion of Implications for Target Population
		160603, 160902, 161101, 161503, 161504, 161403 and 161505.
Due to cumulative effects	In clinical trials, 75 subjects have received less than10 infusions,132 subjects have received 10 to 30 infusions; 70 subjects have received more than 31 to 60 infusions and 37 subjects received more than 60 infusions of HyQvia.	No safety concerns have been observed in clinical trials which are attributed to the effects of cumulative usage of HyQvia. Data on the long-term local and systemic effects of HyQvia were collected during the clinical trial studies 160602, 160603, 160902, 161101, 161503, 161504, 161403, 161505.
Which have a long latency	The length of follow-up observation periods differs depending on clinical trial protocol.	Subjects have been observed during designated follow-up time periods, and there have been no notable ADRs which have occurred with latent onset.

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and breast-feeding mothers. Immunoglobulin products have been shown to cross the placenta, increasingly during the third trimester. Clinical experience with immunoglobulins suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected. Development and reproductive toxicology studies have been conducted with recombinant human hyaluronidase in mice and rabbits. No adverse effects on pregnancy and foetal development were associated with anti-rHuPH20 antibodies. In these studies, maternal antibodies to recombinant human hyaluronidase were transferred to offspring in utero. The effects of antibodies to the recombinant human hyaluronidase component of HyQvia on the human embryo or on human foetal development are currently unknown. The Company has conducted study 161301 (Pregnancy Registry in US and EU) to obtain long-term safety data on both mother and child in the event of pregnancy exposure to HyQvia. The last patient out from the
Breast-feeding women	

Type of special population	Exposure
	pregnancy registry (US and EU study 161301) was in December-2019. HyQvia was evaluated in 9 mothers (4 mothers before delivery and 5 mothers after delivery), 7 in the HyQvia arm and two in the alternative product arm. In addition, 7 infants were enrolled (5 in the HyQvia arm and 2 in the alternative product arm). Four mothers were tested for anti-rHuPH20 binding or neutralizing antibodies and no antibodies were detected. Immunoglobulins are excreted into the milk and may contribute to protecting the neonate from pathogens which have a mucosal portal of entry.
Children	HyQvia was evaluated in 122 paediatric patients with an overall safety experience equivalent to 157.26 patient-years (as described in section Clinical trial exposure Table SIII.2). No appreciable differences in the pharmacodynamic effects or efficacy and safety of HyQvia were observed between paediatric patients and adults. A prospective, Phase 4, multicentre study (161504) in Europe conducted by the Company evaluated 42 paediatric subjects (age 2 to <18 years) who had received prior immunoglobulin therapy. No new safety concerns were identified. No subject was positive (titer ≥160) for binding antirHuPH20 antibodies. HyQvia was found to be safe and tolerable among paediatric subjects (2 to <18 years old) with PIDD.
Elderly	There are limited clinical data in geriatric patients over the age of 65 years; this age group was represented by a total of 36 subjects in clinical trials. However, the safety profile of the product is not expected to differ in this age group from that of younger adults.
Fertility	There are currently no clinical safety data for HyQvia on fertility available. Clinical experience with immunoglobulins suggests that no harmful effects of IG 10% on fertility are to be expected. Animal studies do not indicate direct or indirect harmful effects of rHuPH20 with respect to reproductive potential at the doses used for facilitating administration of IG 10%.
Patients with relevant co-morbidities: - Patients with hepatic impairment - Patients with renal impairment - Patients with cardiovascular impairment - Immunocompromised patients - Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program. Limited clinical data are available in patients with organ impairment (e.g., renal, liver, or cardiac) since these subjects have been routinely excluded from participation in clinical trials.
Population with relevant different ethnic	Clinical studies with HyQvia did not exclude subjects

Type of special population	Exposure
origin	based on race or ethnic origin; however, the majority (296) of participating subjects were White/ Caucasian, with 3 Asian subjects, 2 American Indian or Alaska Native each, 4 Black/ African American, 4 of multiple, 1 of other ethnicities/racial origin and ethnic origin was not reported for 4 subjects. The target indications for HyQvia are known to occur in various ethnic and racial groups. It is unlikely that the safety of HyQvia is affected by race or ethnicity. There are no contraindications for use of HyQvia in patients of any racial or ethnic origin.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.

Part II: Module SV - Post-authorisation experience

SV.1. Post-authorisation exposure

SV.1.1. Method used to calculate exposure

The Company calculates the patient exposure based on estimates on yearly immunoglobulin dose per patient published in 3 difference sources:

The Immunoglobulin Diagnosis, Evaluation, and key Learnings (IDEaL) patient registry is an observational registry directed at the use of immunoglobulin in the USA and sponsored by Coram Clinical Trials, a provider of clinical research services for Phase 1-4 clinical trials. According to IDEaL, a 2009 industry report found that approximately 55% of IGIV was prescribed for non- Food and Drug Administration (FDA) approved indications. Overall (approved and off-label use), approximately 38,500 kg of IGIV were administered to approximately 85,100 patients in the US in 2009, with an average administration of 453 g per patient per year. Sixty percent of the patients (and 67% of total grams used) were treated for 7 diseases: primary immune deficiencies (~525 g/patient/year), chronic inflammatory demyelinating polyneuropathy (~840 g/patient/year), idiopathic thrombocytopenia purpura (~331 g/patient/year), CLL (~420 g/patient/year), and Kawasaki disease (~40 g/patient/year).

The first national immunoglobulin database report 2008-2009 was published in January-2010 by the British Department of Health, on the current prescribing practice of immunoglobulin in England. It was stated that the highest consumption found in a given group of patients was approximately 400 g/patient/year.

A literature article published in 2011 by Khan et al., describing the relationship between immunoglobulin dose and serum IgG level in relation to body size. Analysis of data from 107 patients with CVID who received immunoglobulin replacement therapy in 2007-2008 revealed an annual immunoglobulin dose given of 456 ± 129 g, which equated to mean of 383 ± 188 mg/kg given every 3 weeks[redacted].

Based on published yearly doses and pursuing a conservative approach, Takeda assumes an average treatment dose of 40 g per patient per month. The estimated patient exposure is calculated utilizing the following formula:

The table below presents cumulative patient exposure:

$$\text{Number of patients exposed per month} = \frac{\text{Number of grams sold per period}}{\text{40 g per month X Number of months for period}}$$

SV.1.2. Exposure

Based on the above methodology, cumulative global patient exposure since the international birth date is estimated to be approximately 31,940,434 grams corresponding to approximately 6,022 patients exposed per month. Since post-marketing exposure is based on shipment data, it is not currently possible to break down the patient exposure by region, indication, gender, age, or other factors.

Table SV.1: Cumulative Sales of HyQvia (16-May-2013 to 31-May-2024)*

	Cumulative
Units distributed (grams)	31,940,434
Estimated number of patients exposed per month	6,022

*Cumulative average of the estimated number of unique patients exposed during the given period of time.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There is no known potential for misuse of HyQvia for illegal purposes.

Part II: Module SVII - Identified and potential risks

SVII.1. Identification of safety concerns in the initial RMP submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	Risk-benefit impact
Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	True allergic reactions to HyQvia are rare, but can occur, especially in people with IgA deficiency. Although it is rare, medicines that contain human immunoglobulins can sometimes cause a fall in blood pressure with anaphylaxis (a severe allergic reaction in which a person stops breathing or their heart stops beating and is potentially fatal). This can happen even in patients who have previously received immunoglobulin treatment without negative side effects.
Altered immune response: • Reduced efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella • Interference with serological testing after infusion of immunoglobulin	For 6 weeks to 3 months after treatment with immunoglobulins, the effectiveness of live virus vaccines can be decreased. This includes vaccines that prevent measles, mumps, German measles, and chicken pox. For the measles vaccine, this effect can last up to a full year. Since HyQvia is made from blood components of other people, it may contain various types of antibodies which can be passed along to the HyQvia patient's blood. Some of these antibodies can interfere with certain types of blood tests which test for red blood cell antibodies.
Infusion site reactions (infusion site leaking)	Infusion site reactions are the most common type of reactions seen in patients who receive treatment with HyQvia.
Thromboembolic events (TEEs)	Blood clots have occurred in patients who were given immunoglobulin treatment, either IV (infused into the vein) or SC (infused under the skin). Certain risk factors make it more likely for a person to develop a blood clot, including old age, high blood pressure, diabetes, heart disease, previous blood clots, blood clotting disorders, lack of physical activity, dehydration, or a thick consistency of the blood.
Haemolysis/Haemolytic anaemia	Immunoglobulin medicines may contain antibodies to certain blood groups which can cause the red blood cells to be attacked and broken down by these antibodies. If too many red blood cells are broken down, a person can develop a special type of anaemia, called haemolytic anaemia.
Aseptic meningitis syndrome	Aseptic meningitis syndrome has been reported

Important Identified Risks	Risk-benefit impact
	to occur in association with IV and SC immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following immunoglobulin treatment. Discontinuation of immunoglobulin treatment may result in remission of Aseptic Meningitis Syndrome (AMS) within several days without sequelae. Cerebrospinal fluid studies are frequently positive with pleocytosis up to several thousand cells per mm^3, predominantly from the granulocytic series, and elevated protein levels up to several hundred mg/dL. AMS may occur more frequently in association with high dose (2 g/kg) IV immunoglobulin treatment. From post-marketing data no clear correlation of AMS to higher doses was observed. Higher incidences of AMS were seen in women.

Important Potential Risks	Risk-benefit impact
Transmissible infectious agents	Since HyQvia is made from pools of human plasma, it is possible that it could contain organisms that cause infection, which can be passed on through the medication. Several preventive measures are used when making HyQvia in order to remove infectious organisms, but the possibility of this occurring cannot be completely ruled out.
Spread of localised infection	When a medication is injected into an area where an infection exists, it is possible that the infection could spread.
Renal dysfunction/failure	Some people who have received immunoglobulins through the vein (IV) have experienced kidney failure. In most of these cases, the person had other health issues which could lead to kidney failure.
Drug administration error: incorrect sequence of administration of products	The HyQvia kit contains 2 separate vials of medicine. In order for HyQvia to work properly, the recombinant human hyaluronidase must be given first, and the IG 10% must be given second. It is possible that a person could give the vials in the incorrect order.

Missing Information	Risk-benefit impact
Limited information on safety in pregnant and lactating women	The Company has conducted study 161301 (Pregnancy Registry in US and EU) to obtain long-term safety data on both mother and child in the event of pregnancy exposure to HyQvia. The last patient out from the pregnancy registry (US and EU study 161301) was in December-2019.

Missing Information	Risk-benefit impact
	While the limited data from 161301 does not suggest a different safety profile for pregnant and lactating women, the low number of participants in the study makes it difficult to draw conclusions for 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	Given cumulative data from studies 160603/160902 and as presented in the Summary of Product Characteristics (SmPC) and company core data sheet (CCDS), HyQvia was evaluated in 24 paediatric patients, including 13 patients between 4 and < 12 years and 11 between 12 and < 18 years, who were treated for up to 3.3 years with an overall safety experience equivalent to 48.66 patient-years. No appreciable differences in the pharmacodynamic effects or efficacy and safety of HyQvia were observed between paediatric patients and adults. A prospective, Phase 4, multicentre study (161504) in Europe conducted by the Company evaluated 42 paediatric subjects (age 2 to <18 years) who had received prior immunoglobulin therapy. No new safety concerns were identified. No subject was positive (titre ≥160) for binding antirHuPH20 antibodies. HyQvia was found to be safe and tolerable among paediatric subjects (2 to <18 years old) with PIDD. It is unknown whether it is safe for patients under the age of 18 years to take HyQvia over a long-term period.
Limited clinical data on the influence of the type of PID and CIDP on the immunogenicity of rHuPH20	Some people may produce antibodies (a special type of protein that acts against something in the body) against recombinant human hyaluronidase. It is unknown whether long-term treatment with recombinant human hyaluronidase in HyQvia would lead to any infusion site reactions or body-wide side effects.

SVII.2. New safety concerns and reclassification with a submission of an updated RMP

1. In the Rapporteur Request for Supplementary Information, The Company received the following request from Pharmacovigilance Risk Assessment Committee (PRAC):

> *"Following a member state comment the MAH is asked to evaluate the safety concerns in the summary of safety concerns based on the current criteria of important safety concerns."*

According to Good Pharmacovigilance Practices (GVP) Module V (Rev 2), only those important risks requiring further evaluation and characterisation and/or those requiring specific additional risk minimisation measures should be included [maintained] in the RMP.

HyQvia was first authorised in EU via centralized Procedure on 16-May-2013. After reviewing the available safety information, as presented in the Periodic Benefit Risk Evaluation Report (PBRER), the following important identified risks, important potential risks and missing information will be removed

as these risks are well characterised or additional information is not anticipated; no safety signal has been identified in 10 years of post-marketing experience; and these risks are currently being monitored via routine pharmacovigilance activities (only):

Important identified risks:

- Altered immune response
  - Reduced efficacy of live attenuated virus vaccines such as measles, mumps, rubella, and varicella
  - Interference with serological testing after infusion of immunoglobulin.
- Haemolysis / Haemolytic anaemia.
- Aseptic meningitis syndrome (AMS)

Important potential risks:

- Transmissible infectious agents
- Spread of localised infection
- Renal dysfunction/failure

The remaining risks have either Targeted Questionnaires, additional PV activities or additional risk minimisation measures in place to further characterise and/or minimise the risks.

2. *Following European Medicines Agency's (EMA's) comment dated 16-May-2024 in final assessment Report under procedure EMA/H/C/002491/II/0096), MAH proposes to maintain the missing information "Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20" due to the recent inclusion of CIDP as a new indication for HyQvia. A specific adverse reaction (immunological event) follow-up questionnaire will be included as routine risk minimisation activity concerning this missing information. This is generally accepted.*

   However, in the next RMP update, the MAH is required to include the mentioned follow-up questionnaire concerning "Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20 in patients with CIDP" and update the relevant sections of the RMP accordingly

The "immunological event questionnaire" in Annex 4 addresses the missing information concerning "Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20." Since the questionnaire pertains to the product rather than specific indications, no further update is needed regarding the added indication of CIDP in the "immunological event questionnaire". However, the missing information "Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20" has been re-worded to "Limited clinical data on the influence of the type of PID and CIDP on the immunogenicity of rHuPH20" to include PID and CIDP indications.

SVII.3. Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	
Potential mechanisms:	Immune response to human immunoglobulin therapy.
Evidence source(s) and strength of evidence:	Medical literature, potential mechanism of action
Characterisation of the risk:	Frequency with 95% Confidence Interval Hypersensitivity reactions have been reported in general for IV and SC

[redacted]

Important Identified Risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	
	administered immunoglobulin products. Seriousness/Outcomes Outcomes vary depending on the severity of the allergic/hypersensitivity response or reaction and may result in a serious medical condition or potentially lead to a fatal outcome. Severity and nature of risk Mild hypersensitivity reactions such as a rash may resolve without treatment. However, severe reactions such as anaphylaxis may require significant medical intervention and may very rarely lead to death. Background incidence/prevalence The incidence of anaphylaxis does not appear to vary significantly between countries. Rates globally range from 1-3 cases per 10,000 in the general population[redacted]. However, hypersensitivity drug reactions represent approximately one-third of ADRs, which can affect 7% of the general population and up to 20% of hospitalised patients [redacted]. Hypersensitivity reactions after treatment with IGIV are associated with symptoms that can include local inflammation as well as systemic reactions. Severe anaphylactic reactions can occur in any patient receiving IGIV; however, the risk is increased in patients with selective IgA deficiency who have anti-IgA antibodies in their serum[redacted]. Although these may occur at low frequency (1:20,000 transfusions) [redacted] appropriate monitoring of patients, especially those at high risk, is vital. An increased frequency of allergic manifestations in IgA deficient patients has been previously reported [redacted]. In 2009, Aghamohammadi et al. reported that 19 out of 23 (83%) IgAD patients, aged 4 to 32 years, suffered from allergic diseases including asthma, atopic dermatitis, allergic rhinitis/conjunctivitis, urticaria, drug allergy, or food allergy. The allergic diseases most commonly associated with IgAD are rhino conjunctivitis, urticaria, atopic eczema and bronchial asthma[redacted]. However, the findings are not conclusive, as some studies show no increased frequency of allergies in IgAD subjects and the entity of IgA-related anaphylactic reactions is not evidence based[redacted]. Impact on individual patient The individual impact of such reactions may range from negligible to significant depending on the acuity and severity of the reaction.
Risk factors and risk groups:	The IG 10% component of HyQvia contains trace amounts of IgA. Patients with antibodies to IgA potentially have a greater risk of developing severe hypersensitivity or anaphylactic reactions. One article state that SC immunoglobulin therapy is associated with a less than 1% risk of systemic reactions during infusion [redacted].
Preventability:	If a patient has known anaphylaxis or severe hypersensitivity to human immune globulin, it should be noted in their medical records. Pre-medication with antihistamines may be used for atopic individuals and those with a medical history of allergic reaction. Patients should be informed of the early signs of anaphylaxis/hypersensitivity (e.g., hives, pruritus, generalised urticaria, tightness of the chest, wheezing, and hypotension). If a patient is at high risk, the product should be administered only where supportive care is available for life-threatening reactions.
Impact on the risk-	There is currently no impact of this risk on the risk-benefit balance of the

[redacted]

[redacted]

Important Identified Risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	
benefit balance of the product:	product, as the pharmacovigilance and risk minimisation measures that are in place are considered sufficient at this time.
Public health impact:	None

Important Identified Risk: Infusion site reactions (infusion site leaking)	
Potential mechanisms:	Local tissue inflammation/irritation resulting from SC administration of the medicinal product and leaking of the medicinal product through the skin during physical infusion of the product might occur. Infusion site leaking can result from increased SC tissue pressure caused by rapid infusion, excessive infusion volume, or insufficient dose of recombinant human hyaluronidase. Other reasons could include incorrect needle angle (too shallow) and needle length in relation to the thickness of the SC tissue layer, and the use of infusion sites with insufficient SC tissue to facilitate SC medicinal product administration.
Evidence source(s) and strength of evidence:	Medical literature, clinical trials, potential mechanism of action
Characterisation of the risk:	Frequency with 95% Confidence Interval Local reactions at infusion sites: swelling, soreness, redness, induration, local heat, itching, bruising and rash, may frequently occur. Infusion site leaking can occur during or after SC administration of immunoglobulins, including HyQvia. Seriousness/Outcomes Local reactions associated with administration of HyQvia are relatively common and rarely serious. Severity and nature of risk Local reactions at the infusion site are generally mild and include swelling, soreness, redness, induration, local heat, local pain, itching, bruising, and rash. Background incidence/prevalence The incidence of infusion site and generalised skin reactions after IGSC administration is reported to be as high as 0.584 per infusion [redacted]. Impact on individual patient Depending on severity, local reactions may result in treatment intolerability and discontinuation of the product.
Risk factors and risk groups:	Local reactions are a known risk of any SC infusion.
Preventability:	The occurrence of local reactions may be minimised by infusing the product slowly upon first administration and ensuring that the product is not administered to patients with known sensitivities to human immune globulin. Infusion site leakage (leaking) may be minimised by using longer needles and/or more than one infusion site. Any change of needle size would have to be supervised by the treating physician.
Impact on the risk-benefit balance of the product:	There is currently no impact of this risk on the risk-benefit balance of the product, as the pharmacovigilance and risk minimisation measures that are in place are considered sufficient at this time.
Public health impact:	None

[redacted]

Important Identified Risk: Thromboembolic events (TEEs)	
Potential mechanisms:	Increased viscosity is thought to be an important factor in the development of thromboembolic complications [redacted].
Evidence source(s) and strength of evidence:	SmPC, Company Core Safety Information (CCSI), medical literature, post-marketing reports.
Characterisation of the risk:	Frequency with 95% Confidence Interval Unknown; TEEs have been observed with IG 10% administered IV and SC and cannot be excluded with use of HyQvia. Seriousness/Outcomes The outcome and seriousness of TEEs can vary widely. Deep venous thromboses may resolve spontaneously with little sequelae, while stroke and MI may result in significant disability or death. Severity and nature of risk May potentially result in a serious medical condition or fatal outcome. Background incidence/prevalence The literature indicates that the presence of any single cardiovascular condition does not confer a significant risk of stroke or MI during IGIV infusion, but the risk for TEEs increases as the number of cardiovascular risk factors increase [redacted]. The odds of sustaining a TEE within 2 weeks of IGIV treatment were reported to be ten-fold higher when 4 or more cardiovascular risk factors are present [redacted]. Previous reports examining TEEs associated with IGIV treatment have proposed risk factors including age, cardiovascular risk factors, and first-time exposure of IGIV [redacted]. The frequency of specific TEEs in the general European population are described below: MI: Coronary artery disease is the most common cause of death in the Western world, and most of these deaths are due to MI. Each year approximately 1.5 million patients experience a MI; the annual incidence rate is approximately 600 cases per 100,000 people [redacted]. Stroke: In the UK, approximately 400,000 to 1 million episodes of stroke occur per year [redacted]. Venous thromboembolism: Venous thromboembolism (and/or pulmonary embolism) is a common disorder with an annual incidence of 117 per 100,000 persons [redacted]. Impact on individual patient In the case of severe TEEs, patients may experience disability or life-threating/fatal outcomes requiring inpatient hospital care or long-term treatment.
Risk factors and risk groups:	Patients at increased risk for thrombotic events include those with: • A history of atherosclerosis. • Multiple cardiovascular risk factors. • Advanced age. • Impaired cardiac output. • Hypercoagulable disorders. • Prolonged periods of immobilisation. • Obesity. • Diabetes mellitus. • Acquired or inherited thrombophilic disorder. • A history of vascular disease.

Important Identified Risk: Thromboembolic events (TEEs)	
	• A history of a previous thrombotic or TEE.
Preventability:	If a patient has known risk factors or is part of a risk group for TEEs, it should be noted in the patient records. HyQvia should not be administered at the maximum allowable rate of infusion. Baseline assessment of viscosity should be considered for patients at risk.
Impact on the risk-benefit balance of the product:	There is currently no impact of this risk on the risk-benefit balance of the product, as the pharmacovigilance and risk minimisation measures that are in place are considered sufficient at this time.
Public health impact:	Depending on the severity of the event, patients may require inpatient hospital care.

Important potential risks: Drug administration error: incorrect sequence of administration of products	
Potential mechanisms:	If the two components of HyQvia are administered in the incorrect sequence (i.e., the IG 10% vial is infused prior to the administration of rHuPH20), there will be a decrease in efficacy of the therapeutic component, IG 10%. Infusion of IG 10% by SC route without pre-treatment with rHuPH20 is likely to result in increased infusion pump back pressure.
Evidence source(s) and strength of evidence:	Theoretical risk
Characterisation of the risk:	Frequency with 95% Confidence Interval Unknown. Seriousness/Outcomes Non-serious local infusion site reactions would be expected if the vial of IG 10% were administered before the vial of rHuPH20. Severity and nature of risk Although the immediate impact of the medication error would likely be mild in severity (e.g., localised infusion site reaction), there is a potential for longer term effects if the product is repeatedly administered incorrectly, resulting in insufficient IgG replacement therapy. Infusion of IG 10% by SC route without pre-treatment with rHuPH20 is likely to result in increased local induration and increased infusion pump back pressure (possibly resulting in high pressure alarm activation). High infusion pump pressure may be associated with erythema and vasovagal reactions. Background incidence/prevalence Medication administration errors represent one of the major concerns in patient safety. However, previous studies of medication administration errors focus on errors that occur in the inpatient setting, with major focus on those errors that are the result of healthcare professionals (HCP). This is understandable, due to the fact that it is very difficult to obtain the frequency of outpatient and self-administration errors [redacted]. These types of events are often only captured if the patient is ultimately hospitalised, and even in those instances, it is not recorded as an administration error. Therefore, the exact incidence and prevalence of self-administration medication errors is not known at this time. Impact on individual patient Misadministration may result in decreased efficacy of the therapeutic IG

[redacted]

Important potential risks: Drug administration error: incorrect sequence of administration of products	
	component of the product.
Risk factors and risk groups:	All patients who receive HyQvia therapy are potentially at risk for medication error. However, patients who participate in home administration are at greater risk compared to those who receive therapy under the supervision of an HCP.
Preventability:	Instructions in the SmPC and PIL clearly state the correct order of administration and function of each component of the vial combo. The product labels clearly state that the vial of rHuPH20 is to be infused first and the vial of IG 10% is to be infused second. Additionally, all therapies are to be initiated under the supervision of an HCP.
Impact on the risk-benefit balance of the product:	There is currently no impact of this risk on the risk-benefit balance of the product, as the pharmacovigilance and risk minimisation measures that are in place are considered sufficient at this time.
Public health impact:	None

SVII.3.2. Presentation of the missing information

Missing information: Limited information on safety in pregnant and lactating women	
Evidence source:	While the limited data from the study 161301 does not suggest a different safety profile for pregnant and lactating women, the low number of participants in the study makes it difficult to draw conclusions for safety in pregnant and lactating women. **Population in need of further characterisation:** Use in pregnant or breast-feeding women. The Company has conducted study 161301 (Pregnancy Registry in US and EU) to obtain long-term safety data on both mother and child in the event of pregnancy exposure to HyQvia. The last patient out from the pregnancy registry (US and EU study 161301) was in December-2019. Though small in sample size (9 mothers [4 mothers before delivery and 5 mothers after delivery], 7 in the HyQvia arm and two in the alternative product arm. Four mothers were tested for anti-rHuPH20 binding or neutralizing antibodies and no antibodies were detected).

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	
Evidence source:	The safety of drug in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years has been identified as missing information because limited data about the use of HyQvia in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years is available from the clinical trial development program. Given cumulative data from studies 160603/160902 and as presented in the SmPC and CCDS, HyQvia was evaluated in 24 paediatric patients, including 13 patients between 4 and <12 years and 11 between 12 and < 18 years, who were treated for up to 3.3 years with an overall safety experience equivalent to 48.66 patient-years. No appreciable differences in the pharmacodynamic effects or efficacy and safety of HyQvia were observed between paediatric patients and adults. A prospective, Phase 4, multicentre study (161504) in Europe conducted by the Company evaluated 42 paediatric subjects (age 2 to <18 years)

[redacted]

[redacted]

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	
	who had received prior immunoglobulin therapy. No new safety concerns were identified. No subject was positive (titer ≥160) for binding antirHuPH20 antibodies. HyQvia was found to be safe and tolerable among paediatric subjects (2 to <18 years old) with PIDD **<u>Population in need of further characterisation:</u>** Use in neonates or infants <2 years old. Further characterisation on the effect of prolonged use in patients under the age of 18 years.

Missing information: Limited clinical data on the influence of the type of PID and CIDP on the immunogenicity of rHuPH20	
<u>Evidence source:</u>	It is unknown whether long-term treatment with recombinant human hyaluronidase in HyQvia would lead to any infusion site reactions or body-wide side effects. **<u>Population in need of further characterisation:</u>** Overall, 14 (16.7%) subjects had a positive anti-rHuPH20 antibody result defined as defined as at least one anti-rHuPH20 antibody titer ≥1:160 during treatment. Twenty-four (28.6%) subjects developed low-binding antibodies (abnormal or increased from baseline and <1:160), and 2 subjects had positive neutralizing antibody (NAb). NAb positivity was not associated with treatment-emergent adverse event (TEAE) suggestive of diminished (or absence of) rHuPH20 effect such as prolonged abdominal distention, CIDP relapse, or clinical worsening. There was no reported immune complex mediated local or systemic TEAE such as infusion site induration, or allergic reaction.

[redacted]

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of 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 influence of the type of PID and CIDP on the immunogenicity of rHuPH20.

[redacted]

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Expedited reporting of all TEEs.

Specific adverse reaction follow-up questionnaires for infusion site reactions (infusion site leaking):

Standardized collection of information via leakage or site leaking questionnaire to facilitate better characterisation of the risk.

Specific adverse reaction follow-up questionnaires for thromboembolic events (TEEs):

Standardized collection of information via TEE questionnaire to facilitate better characterisation of the risk.

Specific adverse reaction follow-up questionnaires for important identified risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and for the missing information: Limited clinical data on the influence of the type of PID and CIDP on the immunogenicity of rHuPH20:

Standardized collection of information via immunological event questionnaire to facilitate better characterisation of the risk.

Other forms of routine pharmacovigilance activities:

There are no other forms of routine pharmacovigilance activities ongoing for HyQvia.

III.2. Additional pharmacovigilance activities

There are no additional pharmacovigilance activities ongoing for HyQvia.

III.3. Summary Table of additional Pharmacovigilance activities

Table Part III.1: Ongoing and planned additional pharmacovigilance activities

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				
None.				

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	**Routine risk communication:** SmPC Section 4.3 SmPC Section 4.4 SmPC Section 4.8 Package Leaflet (PL) Section 2 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The following recommendation provided under SmPC section 4.4 and PL section 4: To closely monitor the patients for any symptoms throughout the infusion period, particularly patients starting with therapy. Patients on self-home treatment and/or their guardian should also be trained to detect early signs of hypersensitivity reactions. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Important identified risks: Infusion site reactions (infusion site leaking)	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.8 PL Section 2 PL Section 3 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The following recommendation provided under SmPC section 4.4 and PL section 3: Use longer needles and/or more than one infusion site to avoid infusion site leakage. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Important identified risks: Thromboembolic events (TEEs)	**Routine risk communication:** SmPC Section 4.4 SmPC Section 4.8 PL Section 4

Safety concern	Routine risk minimisation activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: The following recommendation provided under SmPC section 4.4: Patients should be sufficiently hydrated before use of immunoglobulins. Caution should be exercised in patients with pre-existing risk factors for thromboembolic events (such as advanced age, hypertension, diabetes mellitus and a history of vascular disease or thrombotic episodes, patients with acquired or inherited thrombophilic disorders, patients with prolonged periods of immobilisation, severely hypovolemic patients, patients with diseases which increase blood viscosity). Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Important potential risks: Drug administration error - incorrect sequence of administration of products	**Routine risk communication:** SmPC Section 2 SmPC Section 4.2 SmPC Section 4.4 PL Section 3 PL Section 6 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The following recommendation provided under SmPC section 4.4: The recommended infusion rate given in SmPC section 4.2 should be adhered to. Patients must be closely monitored throughout the infusion period, particularly patients starting with therapy. In case of adverse reaction, either the rate of administration must be reduced, or the infusion stopped. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Missing information: Limited information on safety in pregnant and lactating women	**Routine risk communication:** SmPC Section 4.6 PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
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 communication:** SmPC Section 4.2 SmPC Section 4.4 SmPC Section 4.5 SmPC Section 4.6 SmPC Section 4.8

Safety concern	Routine risk minimisation activities
	SmPC Section 5.1 SmPC Section 5.2 PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Missing information: Limited clinical data on the influence of the type of PID and CIDP on the immunogenicity of rHuPH20	**Routine risk communication:** SmPC Section 4.2 SmPC Section 4.8 PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** None proposed.

V.2. Additional Risk Minimisation Measures

Educational materials are proposed as an additional risk minimisation measure.

Objectives	To educate prescribers and users on the correct administration procedure of HyQvia and ensure they are well informed and able to use HyQvia according to the guidance provided in the SmPC and thereby mitigating the risk of Drug administration error.
Rationale for the additional risk minimisation activity	The PRAC requested the MAH to propose educational materials. The focus of the educational materials would be to ensure that the sequence of administration of HyQvia and its excipient human recombinant hyaluronidase is appropriate and as per the SmPC.
Target audience and planned distribution path	The educational materials are aimed at ensuring the appropriate sequence of administration of HyQvia and its excipients, to mitigate the risk of drug administration error in patients who participate in home administration. The MAH shall ensure that in each Member State where HyQvia is marketed, all health care professionals and patients who are expected to use HyQvia have access to/are provided with the following educational material: • **Physician educational material** • **Patient information pack** **Physician educational material**: • The Summary of Product Characteristics • Guide for HCP **Guide for HCPs**: o Information on HyQvia, including the approved indication according to the SmPC. o Detailed description of the administration procedures for

	infusing HyQvia with a syringe driver pump and with a peristaltic infusion pump with counselling points to emphasize with the patient at each process step. - Proper preparation and administration of HyQvia (i.e., infusion of the recombinant human hyaluronidase vial (HY) before the human normal immunoglobulin 10% vial (IG)). - Following aseptic technique. - Identification of early signs and symptoms of potential adverse events (e.g., local infusion site reactions, allergic-type hypersensitivity reactions) and measures to be taken in case reactions occur, including when to contact the HCP. o Patients and/or their caregivers will be asked to demonstrate to the HCP trainer that they can successfully administer HyQvia. Proper technique should be reviewed at regular intervals. o The importance of reporting adverse reactions such as infusion-related reactions and allergic-type hypersensitivity reactions. **The patient information pack**: • Patient information leaflet • A patient/carer guide • A patient diary • **Patient/carer guide**: o A detailed, step-by-step description of the correct preparation and administration technique for infusing HyQvia. o Detailed description for the self-administration, infusion of HyQvia with a syringe driver pump and with a peristaltic infusion pump. o A description of the potential risks(s) associated with the use of HyQvia namely: local infusion site reactions and allergic-type hypersensitivity reactions (signs and symptoms). o Recommendations for managing possible adverse events associated with HyQvia treatment as well as when to contact the HCP. o Importance of reporting adverse events along with instructions on how to report. o Website feature allows for clickable animations to guide patients through administration sequence. • **Patient diary**: o An infusion log will be provided to document the time, date, dose, infusion-site location, and any reactions the patient experiences. o The infusion log will also include a description of precaution(s) needed to minimise the potential adverse events associated with the use of HyQvia. o The infusion log will help facilitate regular monitoring of the patient´s health status and facilitate discussions with the

	HCP.
Plans to evaluate the effectiveness of the interventions and criteria for success	Given the nature of the error, effectiveness will be measured via a detailed review of post marketing data included in the next PBRER (Q2 2025).

V.3. Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

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: Thromboembolic events (TEEs)	**Routine risk minimisation 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Expedited reporting of all TEEs. TEE questionnaire. **Additional pharmacovigilance activities:** None.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL Section 4 **Additional risk minimisation measures:** 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 proposed	**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:** None
Missing information: Limited clinical data on the influence of the type of PID and CIDP on the immunogenicity of rHuPH20	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Immunological Event Questionnaire.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: None.	**Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan

Summary of RMP for HyQvia (Human Normal Immunoglobulin)

This is a summary of the RMP for HyQvia. The RMP details important risks of HyQvia, and how more information will be obtained about HyQvia's risks and uncertainties (missing information).

HyQvia's SmPC and its PL give essential information to HCP and patients on how HyQvia should be used.

This summary of the RMP for HyQvia should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of HyQvia's RMP.

I. The medicine and what it is used for

HyQvia is authorised as:

Replacement therapy in adults, children and adolescents (0-18 years) in:

- Primary immunodeficiency (PID) syndromes with impaired antibody production
- Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/L.

*PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

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

- Chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy after stabilization with intravenous immunoglobulin (IVIg).

Kindly refer SmPC for the full indication. It contains human normal immunoglobulin as the active substance, and it is given by SC route.

Further information about the evaluation of HyQvia's benefits can be found in HyQvia's European Public Assessment Report (EPAR), including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/overview/hyqvia-epar-summary-public_en.pdf

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of HyQvia, together with measures to minimise such risks and the proposed studies for learning more about HyQvia's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCP;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of HyQvia is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of HyQvia are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of HyQvia. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
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 influence of the type of PID and CIDP on the immunogenicity of rHuPH20.

II.B Summary of important risks

Important identified risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	
Evidence for linking the risk to the medicine	Medical literature, potential mechanism of action.
Risk factors and risk groups	The IG 10% component of HyQvia contains trace amounts of IgA. Patients with antibodies to IgA potentially have a greater risk of developing severe hypersensitivity or anaphylactic reactions. One article state that SC immunoglobulin therapy is associated with a less than 1% risk of systemic reactions during infusion. A study of immediate hypersensitivity reactions in 100 healthy volunteers, injected intradermally with 0.1 ml of rHuPH20 solution (150 U/ml), showed absence of reaction in all subjects (Halozyme Study R04-0851).
Risk minimisation measures	**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 monitored the patients throughout the infusion period. SmPC Section 4.8 PL Section 2 **Additional risk minimisation measures:** None.

Important identified risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	
Additional pharmacovigilance activities	None

Important Identified Risk: Infusion site reactions (infusion site leaking)	
Evidence for linking the risk to the medicine	Medical literature, clinical trials, potential mechanism of action
Risk factors and risk groups	Local reactions are a known risk of any SC infusion.
Risk minimisation measures	**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.
Additional pharmacovigilance activities	None

Important Identified Risk: Thromboembolic events (TEEs)	
Evidence for linking the risk to the medicine	SmPC, CCSI, medical literature, post-marketing reports
Risk factors and risk groups	Patients at increased risk for thrombotic events include those with: • A history of atherosclerosis. • Multiple cardiovascular risk factors. • Advanced age. • Impaired cardiac output. • Hypercoagulable disorders. • Prolonged periods of immobilisation. • Obesity. • Diabetes mellitus. • Acquired or inherited thrombophilic disorder. • A history of vascular disease. • A history of a previous thrombotic or TEE.
Risk minimisation measures	**Routine risk minimisation 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

Important Identified Risk: Thromboembolic events (TEEs)	
	Additional risk minimisation measures: None.
Additional pharmacovigilance activities	None

Important potential risks: Drug administration error: incorrect sequence of administration of products	
Evidence for linking the risk to the medicine	Theoretical risk
Risk factors and risk groups	All patients who receive HyQvia therapy are potentially at risk for medication error. However, patients who participate in home administration are at greater risk compared to those who receive therapy under the supervision of an HCP.
Risk minimisation measures	**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 proposed
Additional pharmacovigilance activities	None

Missing information: Limited information on safety in pregnant and lactating women	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.6 and PL Section 2 where fertility, pregnancy and lactation are discussed. **Additional risk minimisation measures:** 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	
Risk minimisation measures	**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

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	
	PL Section 2 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None

Missing information: Limited clinical data on the influence of the type of PID and CIDP on the immunogenicity of rHuPH20	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 SmPC Section 4.8 PL Section 2 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of HyQvia.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for HyQvia.

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Part VII: Annexes

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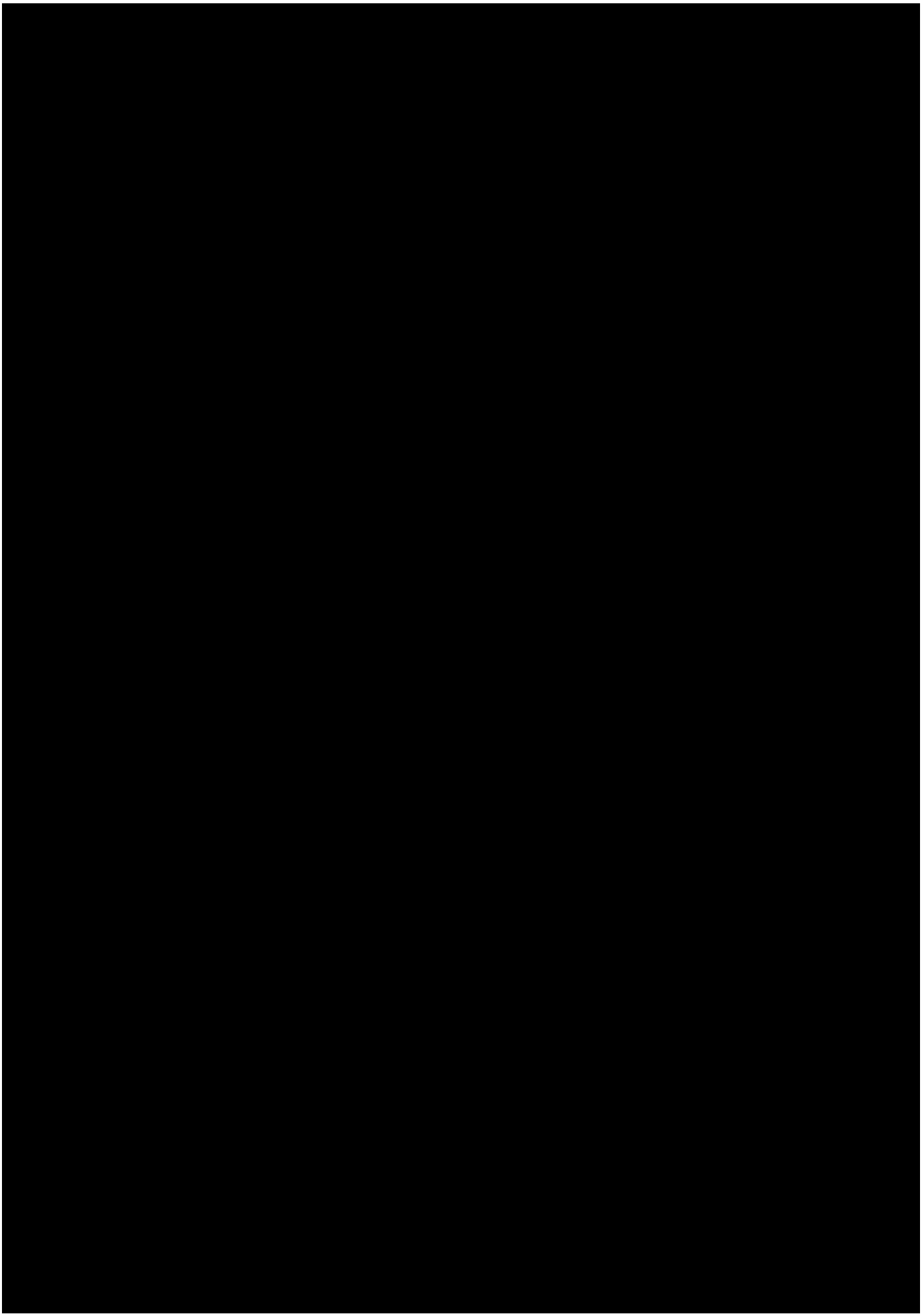
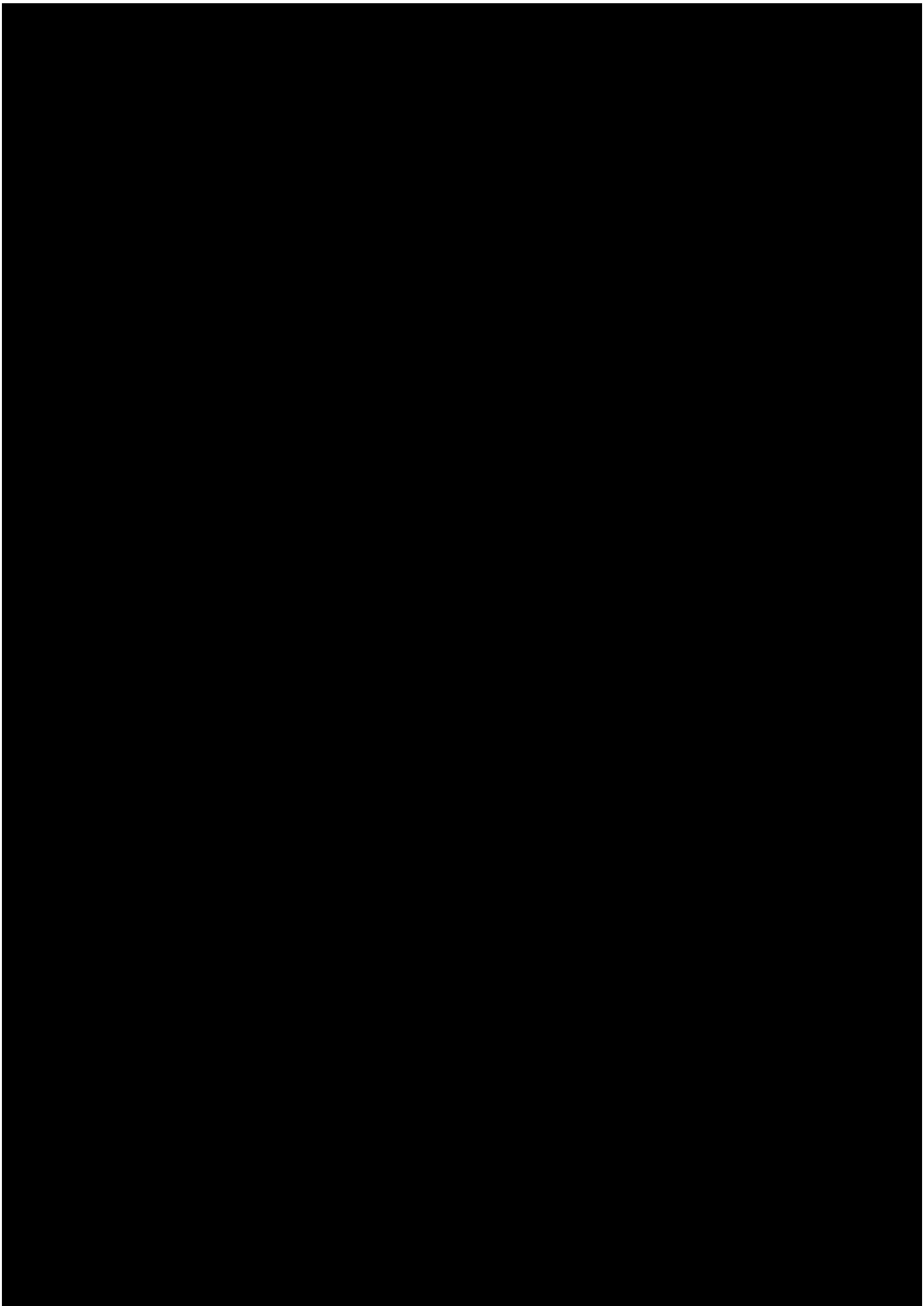




Annex 4: Specific adverse drug reaction follow-up forms

Annex 4.1: The TEE Questionnaire

Annex 4.2: Immunological Event Questionnaire

Annex 4.3: Leakage or Site Leaking Questionnaire

Annex 4.1: The TEE Questionnaire

Case ID: Patient/Study ID:	Send completed questionnaire by email to Takeda at: _____

1. PATIENT INFORMATION

Patient initials: Date of Birth (ddmmmyyyy) or Age: Gender: ☐Male ☐Female ☐Unknown Race: Select One If Other, please specify:	Weight: ☐kg ☐lb Height: ☐cm ☐in Waist circumference:

2. HYQVIA USE

Indication for Use:
Date of first Dose (ddmmmyyyy): Date of Latest Dose (ddmmmyyyy):
Lot number(s) prior to the event onset:
Dose (mg/kg) / Infusion Rate (mL/hr): Frequency:

3. THROMBOEMBOLIC ADVERSE EVENT DESCRIPTION

(Diagnosis, if available: otherwise, list signs and symptoms)
Time of first symptom of thromboembolic event relative to the infusion:
Outcome: Unknown

4. POSSIBLE RISK FACTORS

Cardiac and Vascular Disorders: *(Check all that apply)*

Atherosclerosis	☐	Impaired cardiac output	☐
Angina pectoris	☐	Peripheral vascular disease (PVD)	☐
Previous Angioplasty	☐	PVD with claudication	☐
Cardiac Stress Test abnormal	☐	Unilateral limb swelling	☐
Hypertension	☐	Other Cardiac or vascular disorder	☐ Specify:

Previous Thromboembolic Episodes: *(Check all that apply)*

Previous Thromboembolic event	☐ Specify the year of event:
Previous Myocardial Infarction	☐
Previous Pulmonary Embolism	☐
Previous Stroke	☐
Previous Deep Vein Thrombosis (DVT)	☐
Previous Transient Ischemic Attack	☐
Other (specify):	

Malignancies, Trauma or Surgery: *(Check all that apply)*

Metastatic or active malignant disorder	☐ Please specify:
Trauma or surgery within 4 weeks	☐ Please specify:

Immobilization: *(Check all that apply)*

Case ID: Patient/Study ID:				Send completed questionnaire by email to Takeda at: _____
General (e.g., bedridden or prolonged bed rest > 3 days)	☐			
Limb immobilization (e.g., cast)	☐			
Neurologic (e.g., paralysis or paresis from brain, spinal cord, or neuromuscular disease or injury)	☐			
Other type of immobility	☐ Please specify:			
Inflammatory Disorders: (e.g., Rheumatoid Arthritis, ANCA-associated Vasculitis, Inflammatory Bowel: *(Check all that apply)*				
Current inflammatory disorder	☐ Please specify:			
Infectious Disorders: (e.g., HIV, Pneumonia, Urinary Tract Infection, etc.): *(Check all that apply)*				
Current infectious disorder	☐ Please specify:			
Co-Medications: *(Check all that apply)*				
Current oral contraceptives or hormone replacement therapy	☐ Please specify:			
Current lipid lowering therapy	☐ Please specify:			
Hypercoagulable Disorders (including Paraproteins): *(Check all that apply)*				
Factor V Leiden	☐	Protein C deficiency	☐	
Paraproteins	☐	Elevated plasma homocysteine levels	☐	
Antiphospholipid antibodies	☐	Antithrombin deficiency	☐	
Protein S deficiency	☐			
Other inherited hypercoagulable condition	☐ Please specify:			
Other Risk Factors: *(Check all that apply)*				
Current Smoker	☐	Hyperlipidemia	☐	
Hyperthyroidism	☐	In-dwelling venous catheter	☐	
Other risk factors (please specify):				

5. MEDICAL HISTORY / CONCOMITANT DISEASES

Please specify any other medical history, concomitant disease and concurrent medication below.

Diagnosis	State Date (ddmmmyyyy)	Stop Date (ddmmmyyyy)	Check if Ongoing?
			☐
			☐
			☐
			☐
			☐

[redacted]

Case ID: Patient/Study ID:	Send completed questionnaire by email to Takeda at: _____

CONCOMITANT MEDICATIONS

Trade / Generic Name	Dose / Frequency/ Route of Administration	Indication	Start Date (ddmmmyyyy)	Stop Date (ddmmmyyyy)	Check if Ongoing?
	Dose: Route: Freq:				☐
	Dose: Route: Freq:				☐
	Dose: Route: Freq:				☐
	Dose: Route: Freq:				☐
	Dose: Route: Freq:				☐
	Dose: Route: Freq:				☐

6. ADDITIONAL COMMENTS

QUESTIONNAIRE COMPLETED BY	Printed Name:	Today's Date:
	Signature:	
	Address:	
	Contact Number:	Email:

[redacted]

[redacted]

Annex 4.2: Immunological Event Questionnaire

[redacted]

Case ID: Patient/Study ID:	Send completed questionnaire by email to Takeda at: _____

1. PATIENT INFORMATION

Patient initials:	
Date of Birth or Age	Date (ddmmmyyyy): Or Age:
Gender:	☐Male ☐Female ☐Unknown
Race:	Select One If Other, please specify:

2. HYQVIA USE

Indication for Use (type of PID):

☐CVID
☐IgG subclass deficiency
☐Wiskott Aldrich Syndrome
☐Antibody deficiency
☐Hyper IgM Syndrome
☐X-linked agammaglobulinaemia
☐Severe Combined Immune Deficiency
☐Other PID If Other, please specify:
☐Immunomodulation, specify disease indication:

Date of first Dose (ddmmmyyyy):		Date of Latest Dose (ddmmmyyyy):	
Lot number(s) prior to the event onset:			
Dose / Infusion Rate:		Frequency:	

3. ADVERSE EVENT DESCRIPTION

(Diagnosis, if not available: signs and symptoms)

Primary Adverse Event

☐Treatment with HyQvia was continued after Adverse Event remission

☐Treatment with HyQvia was interrupted due to the following Adverse Event(s)

Signs and Symptoms

Presence of any of the following signs and symptoms (individually or in combination) raises the possibility of an immune mediated reaction.

Please check all of the below signs and symptoms observed:

Local Reactions

☐Redness
☐Itching
☐Urticaria
☐Induration
☐Blistering of the Skin
☐Thickening or Scaling of the Skin
☐Persistent Nodules at site(s)

Systemic Reactions

☐Urticaria
☐Tightness in Throat
☐Generalized Itching (esp. groin or axillae)
☐Hoarseness

Case ID: Patient/Study ID:	Send completed questionnaire by email to Takeda at: _____

☐Swelling in Mouth	☐Itching in mouth or throat
☐Chest Tightness	☐Wheezing
☐Fall in Blood Pressure	☐Fainting/Loss of Consciousness
☐Cyanosis	☐Cold Clammy Skin
☐Nausea	☐Myalgia

4. LABORATORY TESTS

CBC: ☐No ☐ Yes Results (esp eosinophilia):
Complement: ☐No ☐Yes CH50: C3: C4:
Immune Complexes: ☐No ☐Yes
PolyEthylene Glycol precipitation-complement consumption assay (PEG):
Human lymphoblastoid cell line (Raji) radioimmune assay:
Tryptase: ☐No ☐Yes Results:
Histamine Levels: ☐No ☐Yes Results:
Biopsy: ☐No ☐Yes Results:
Anti-rHuPH20 antibody titer: ☐No ☐Yes Results: Date (ddmmmyyyy):

5. TIMELINES and Treatment

Did the patient require:	ER visit? ☐No ☐Yes Hospitalization? ☐No ☐Yes How long?
Was Treatment Given?	☐No ☐Yes
Antihistamines	☐No ☐Yes ☐IV ☐Oral ☐IM
Steroids	☐No ☐Yes ☐IV ☐Oral ☐Topical
Epinephrine	☐No ☐Yes ☐IV ☐Oral ☐IM
Oxygen	☐No ☐Yes

When did symptoms begin in relation to infusion:

Outcome: Select One
Comment:

6. MEDICAL HISTORY / CONCOMITANT DISEASES

Diagnosis	State Date (ddmmmyyyy)	Stop Date (ddmmmyyyy)	Check if ongoing
			☐
			☐
			☐
			☐
			☐
			☐
			☐

[redacted]

Case ID: Patient/Study ID:			Send completed questionnaire by email to Takeda at: _____
			☐

7. ADDITIONAL COMMENTS		
QUESTIONNAIRE COMPLETED BY	Printed Name:	Today's Date:
	Signature:	
	Address:	
	Contact Number:	Email:

[redacted]

Annex 4.3: Leakage or Site Leaking Questionnaire

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at:** _____
Only to be completed by Takeda staff	
Email Address:	Country:
Patient ID:	Date of Birth (ddmmmyyyy):
Suspect Product(s):	

1. CALL DEMOGRAPHICS		
Reporter Name	Date of report (ddmmmyyyy)	Date of Event (ddmmmyyyy)
☐ HCP or ☐Consumer If HCP, indicate profession:		

2. PATIENT DEMOGRAPHICS			
Patient Initials	Date of birth (ddmmmyyyy)	Weight (kg/lb)	Height (ft / Inches /cm)
		kg☐ lb☐	ft☐ in☐ cm☐

3. PRESCRIBING / ADMINISTRATION DEMOGRAPHICS			
Ordering HCP / Contact Info:	Nurse Agency / Contact Info:	Site of Infusion:	Who Administered:
		Select One If Other, specify:	Select One If Other, specify:

4. DOSING INFORMATION				
HyQvia Lot #:		Infusion# for Patient:		☐ Check if treatment with HyQvia new to patient
Indicate how many previous infusions were completed without extravasation/leakage?				
Dose ordered (grams):		Dose Frequency Planned Every:	☐2 weeks ☐ 3 weeks ☐4 weeks Other:	

5. NEEDLE DEMOGRAPHICS			
Needle Length:	Needle Gauge:	Needle Brand:	Needle Set Type:
Select One If Other, specify:	☐ 24 Gauge ☐ Other, specify:	☐ HigHFlow (RMS) ☐ FlowEase (Baxter) ☐Other, specify:	☐ Single ☐Bifurcated ☐Other, specify:

6. PUMP DEMOGRAPHICS		
Pump Type	Pump Brand / Manufacturer	Occlusion Pressure
☐Syringe Driver ☐Peristatic		What is the Occlusion Pressure set at? (PSI/mmHg):

7. EVENT DESCRIPTION	
Was the needle set leaking? Was the needle set broken? Was the administration site leaking?	☐Yes ☐No ☐Unknown ☐Yes ☐No ☐Unknown ☐Yes ☐No ☐Unknown
Was all the Recombinant Human Hyaluronidase (HY) that came	☐Yes ☐No ☐Unknown

[redacted]

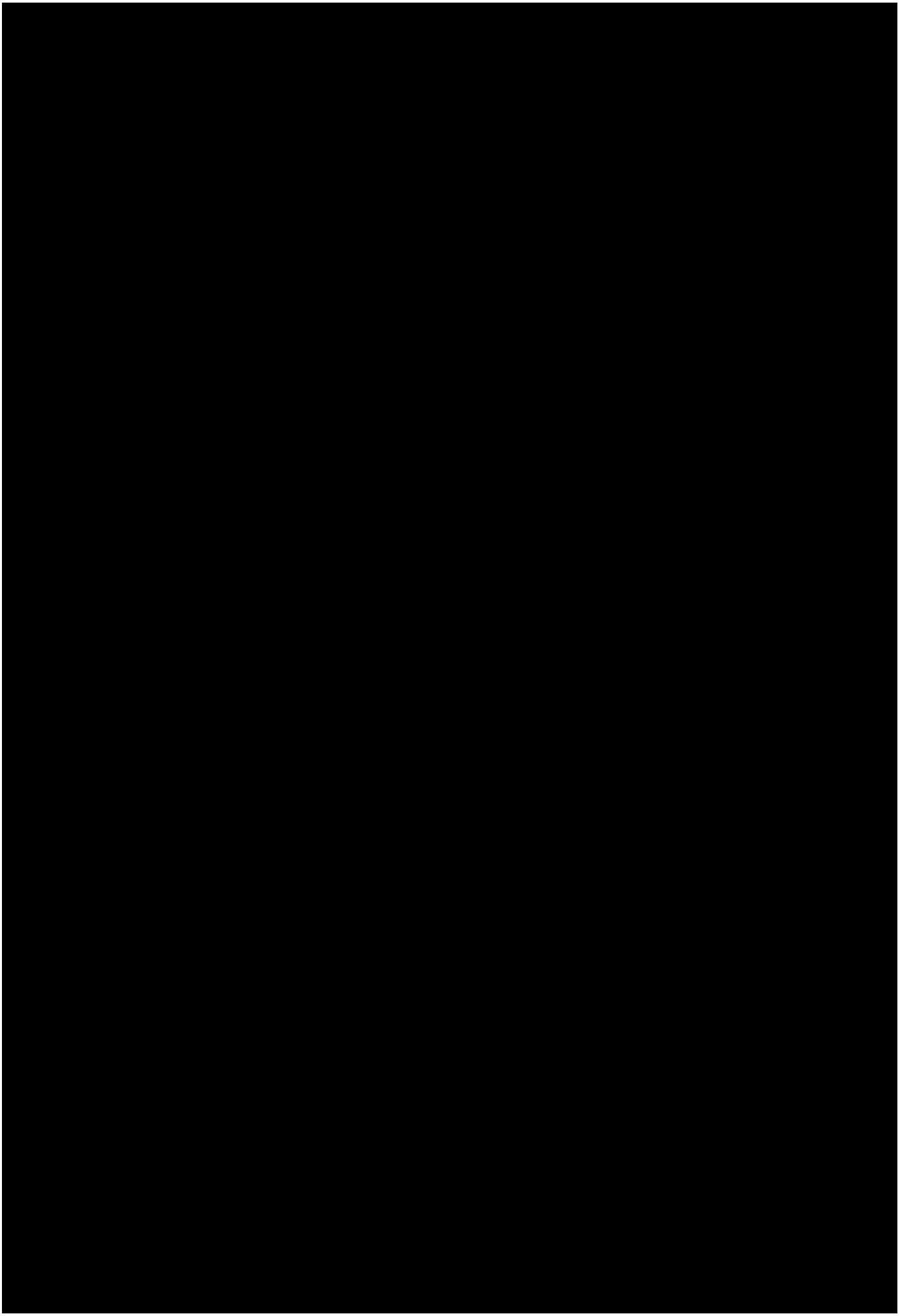
Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at:** _____

with each vial of IG infused prior to the IG?		If no, how much was infused? mL
How long after the HY was infused did the IG infusion start (in minutes)?		Minutes
Did leaking occur during infusion or after?	☐During ☐ After	
If leaking started after completion of infusion?	☐ Immediately post infusion as soon as dressing came off ☐ Well after completion of infusion	
How long did leaking continue?	Minutes: Hours: Days:	
At what infusion rate did the leaking occur?	ml/hr/site	
How much was infused at the time leaking started?	mL or grams	
What was the total intended dose to be infused?	mL or grams	
If using a bifurcated set, were both sites leaking?	☐Yes ☐No ☐Unknown Comments:	
Did the needle move or dislodge during infusion?	☐Yes ☐No ☐Unknown	
Were the butterfly wings lying flat on the skin during infusion?	☐Yes ☐No ☐Unknown	
Did the dressing come loose during the infusion?	☐Yes ☐No ☐Unknown	

8. ADDITIONAL COMMENTS

QUESTIONNAIRE COMPLETED BY	Printed Name:	Today's Date:
	Signature:	
	Address:	
	Contact Number:	Email:

[redacted]



Annex 6: Details of proposed additional risk minimisation activities

Prior to the launch (where applicable) or use of HyQvia in each Member State the MAH must agree about the content and format of the programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational materials are aimed at ensuring the appropriate sequence of administration of HyQvia and its excipients, to mitigate the risk of drug administration error in patients who participate in home administration.

The MAH shall ensure that in each Member State where HyQvia is marketed, all health care professionals and patients who are expected to use HyQvia have access to/are provided with the following educational material:

- **Physician educational material**
- **Patient information pack**

Physician educational material:

- The Summary of Product Characteristics
- Guide for HCPs

Guide for HCPs:

- Information on HyQvia, including the approved indication according to the SmPC
- Detailed description of the administration procedures for infusing HyQvia with a syringe driver pump and with a peristaltic infusion pump with counselling points to emphasize with the patient at each process step
    - Proper preparation and administration of HyQvia (i.e., infusion of the recombinant human hyaluronidase vial before the human normal IG 10% vial
    - Following aseptic technique
    - Identification of early signs and symptoms of potential adverse events (e.g., local infusion site reactions, allergic-type hypersensitivity reactions) and measures to be taken in case reactions occur, including when to contact the HCP
- Patients and/or their caregivers will be asked to demonstrate to the HCP trainer that they can successfully administer HyQvia. Proper technique should be reviewed at regular intervals.
- The importance of reporting adverse reactions such as infusion-related reactions and allergic-type hypersensitivity reactions

The patient information pack:

- Patient information leaflet
- A patient/carer guide
- A patient diary
- **Patient/carer guide**:
    - A detailed, step-by-step description of the correct preparation and administration technique for infusing HyQvia
    - Detailed description for the self-administration, infusion of HyQvia with a syringe driver pump and with a peristaltic infusion pump
    - A description of the potential risks(s) associated with the use of HyQvia namely: local infusion site reactions and allergic-type hypersensitivity reactions (signs and symptoms)
    - Recommendations for managing possible adverse events associated with HyQvia treatment as well as when to contact the HCP

- Importance of reporting adverse events along with instructions on how to report
- Website feature allows for clickable animations to guide patients through administration sequence.

- **Patient diary**:
  - An infusion log will be provided to document the time, date, dose, infusion site location, and any reactions the patient experiences
  - The infusion log will also include a description of precaution(s) needed to minimise the potential adverse events associated with the use of HyQvia
  - The infusion log will help facilitate regular monitoring of the patient´s health status and facilitate discussions with the HCP