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EU RISK MANAGEMENT PLAN (RMP)

for

HyQvia (Human Normal Immunoglobulin)

RMP Version number: 15.0

Date: 21-November-2023

[redacted]

[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: 15.0

Data lock point (DLP) for this RMP: 31-May-2023

Date of final sign off: 21-November-2023

Rationale for submitting an updated RMP: The RMP is being updated to include the completion and submission of study 161406 – Non-Interventional Post- Marketing Safety Study on the Long-Term Safety of HyQvia (Global).

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Updated additional monitoring in EU to "No".
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 exposure as of DLP. In addition, clinical trial exposure added separately indication wise for "Primary immunodeficiency syndromes (PID)" and "Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)" indications in addition to exposure by all indications.
Module SIV Populations not studied in clinical trials	Not applicable.
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	Removed the MedDRA search terms to align with EMA template.
Module SVIII Summary of the safety concerns	Not applicable.
Part III Pharmacovigilance plan	Studies 161406 and 161503 were completed, hence, removed as additional pharmacovigilance activities.
Part IV Plans for post-authorisation efficacy studies	Not applicable.
Part V Risk minimisation measures	Studies 161406 and 161503 were completed, hence, removed as additional pharmacovigilance activities
Part VI Summary of the risk management	Studies 161406 and 161503 were completed,

[redacted]

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RMP Module:	Significant Changes:
plan	hence, removed as additional pharmacovigilance activities.
Part VII Annexes	Annex 1 added as per template. Annex 2: Moved studies 161406 and 161503 from ongoing to completed. Annex 3: Removed the completed studies 161406 and 161503.

Other RMP versions under evaluation:

RMP Version no. 14.3

Submitted on: 21-November-2023

Approved with procedure: under evaluation with procedure EMEA/H/C/002491/II/0087

Details of the currently approved RMP:

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QPPV name: Stéphane Brouckaert, MPharm

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

QPPV signature: [redacted]

[redacted]

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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
CJD	Creutzfeldt-Jakob Disease
CLcr	Creatinine Clearance
CLL	Chronic lymphocytic 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
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practice
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCP	Healthcare Professionals
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High-Level Terms
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

[redacted]

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)
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MM	Multiple Myeloma
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
PI	Product Information
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
PT	Preferred Term
rHuPH20	Recombinant Human Hyaluronidase
RMP	Risk Management Plan
SC	Subcutaneous(ly)
SID	Secondary Immunodeficiencies
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SOC	System Organ Class
TEE(s)	Thromboembolic Event(s)
TK	Toxicokinetic(s)

[redacted]

Abbreviation	Definition/Description
TVR	Triple Virally Reduced
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organisation

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
	Summary of mode of action: The immune globulin infusion (Human) 10% (IG 10%) component provides the therapeutic effect of this medicinal product. The recombinant human hyaluronidase facilitates the dispersion and absorption of IG 10%. Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of opsonising and neutralising 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 1,000 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. Recombinant human hyaluronidase is a soluble recombinant form of human hyaluronidase that increases the permeability of the SC 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 recombinant human hyaluronidase increases permeability of the SC tissue by temporarily depolymerizing hyaluronan. The recombinant human hyaluronidase of HyQvia acts locally. The effects of the hyaluronidase are reversible, and permeability of the SC tissue is restored within 24 to 48 hours.

[redacted]

	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.
	Proposed: Not applicable.
Dosage in the EEA	Current: The medicinal product should be administered via the SC route. In replacement therapy the dose may need to be individualized for each patient dependent on the pharmacokinetic and clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients. The following dosage regimens are given as a guideline: *Replacement therapy in primary immunodeficiency syndromes* *Patients naïve to immunoglobulin therapy* The dose required to achieve a trough level of 6 g/L is of the order of 0.4-0.8 g/kg body weight per month. The dosage interval to maintain steady state levels varies from 2-4 weeks. 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 dosage and aim for higher 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.

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	Patients previously treated with immunoglobulin administered intravenously: For patients switching directly from intravenous administration of immunoglobulin, or who have a previous intravenous dose of immunoglobulin that can be referenced, the medicinal product should be administered at the same dose and at the same frequency as their previous intravenous immunoglobulin 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 immunoglobulin administered subcutaneously:* For patients currently being administered immunoglobulin SC, the initial dose of HyQvia is the same as for SC treatment but may be adjusted to 3- or 4-weeks interval. The first infusion of HyQvia should be given one week after the last treatment with the previous immunoglobulin. *Secondary immunodeficiencies* The recommended dose is 0.2-0.4 g/kg every 3-4 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. *Paediatric population* The posology in children and adolescents (0-18 years) is not different to that of adults as the posology for each indication is given by body weight and adjusted to the clinical outcome of the above-mentioned condition.
	Proposed: Not applicable.
Pharmaceutical form(s) and strengths	Current: <u>Pharmaceutical form</u> - 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). One mL contains 100 mg of Human normal immunoglobulin (purity of at least 98% IgG). IG 10% is a clear or slightly opalescent and colourless or pale-yellow solution. Recombinant human hyaluronidase is a clear, colourless solution. <u>Strengths</u> The HyQvia dual vial system is available in the following volume combinations:

rHuPH20	**Human normal immunoglobulin**	
Volume (mL)	**Protein (g)**	**Volume (mL)**
1.25	2.5	25
2.5	5	50
5	10	100
10	20	200
15	30	300

[redacted]

[redacted]

	Proposed: Not applicable.
Is/will the product be subject to additional monitoring in the EU?	No

[redacted]

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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.

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Primary immunodeficiency syndromes	
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 options:	Treatment will depend on the type of PIDD. Patients who suffer from 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 aetiology 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[redacted]. 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[redacted]. 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%)[redacted]. 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 [redacted].
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%)[redacted] Nearly one-third of patients also report frequent diarrhoea 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[redacted]. 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 [redacted]. Represented by over 80 heterogeneous

[redacted]

[redacted]

Primary immunodeficiency syndromes	
	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[redacted]. In patients with PIDD, autoimmunity occurs at a significantly higher incidence commonly appearing as the first presentation of immune deficiency [redacted]. 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%), 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 that 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

[redacted]

[redacted]

Secondary Immunodeficiencies	
	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 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

[redacted]

[redacted]

Secondary Immunodeficiencies	
	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 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	SID can occur in adults, children and adolescents. Both male

[redacted]

[redacted]

Secondary Immunodeficiencies	
population in the indication:	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 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 enema, 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,

[redacted]

[redacted]

Secondary Immunodeficiencies	
	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 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

[redacted]

[redacted]

Secondary Immunodeficiencies	
	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].

[redacted]

[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 to the human IgG preparation and

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Study		Relevance for Human Usage
		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 performed from plasma

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Study		Relevance for Human Usage
		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 units (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 disruption or degradation of hyaluronic acid in

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Study		Relevance for Human Usage
		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 Behavioural/ 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 Study Design).	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 development from late gestation through adulthood does not result in adverse effects

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Study		Relevance for Human Usage
		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 chronic subset. There were observations of

[redacted]

Study		Relevance for Human Usage
		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 impact of anti-

[redacted]

Study		Relevance for Human Usage
		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	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.

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Study		Relevance for Human Usage
	10% with 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

[redacted]

Part II: Module SIII - Clinical trial exposure

Table SIII.1: Duration of exposure by indication

Cumulative for all indications (person time)*:		
Duration of exposure	**Patients**	**Person time (years)**
0 to <0.5 years	172	37.00
0.5 to <1 year	25	15.48
1 to <2 years	114	154.80
2 to <3 years	49	126.03
3 or more years	54	195.12
Total person time	**414**	**528.43**

*The data cut-off used for this table was 31-May-2023.
Indication: Cumulative - Studies 160602, 160603, 160902, 161001 (Healthy Volunteers), 161101, 161503, 161504, 170901 - Part 4, 161403, 161505, TAK771-1001 (Healthy Volunteers).

Indication-PID (person time)*:		
Duration of exposure	**Patients**	**Person time (years)**
0 to <0.5 years	104	15.64
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	**263**	**309.55**

*The data cut-off used for this table was 31-May-2023.
PID = Primary immune deficiency.
Indication: PID - Studies 160602, 160603, 160902, 161001 (Healthy Volunteers), 161101, 161503, 161504, 170901 - Part 4.

Indication-CIDP (person time)*:		
Duration of exposure	**Patients**	**Person time (years)**
0 to <0.5 years	68	21.36
0.5 to <1 year	12	6.46
1 to <2 years	20	30.81
2 to <3 years	28	67.08
3 or more years	23	93.17
Total	**151**	**218.88**

*The data cut-off used for this table was 31-May-2023.
CIDP = Chronic inflammatory demyelinating polyradiculoneuropathy.
Indication: CIDP - Studies 161403, 161505, TAK771-1001 (Healthy Volunteers).

[redacted]

Table SIII.2: Age group and gender by indication

Cumulative for all indications: age/gender groups (person time)*:						
Age group	**Patients**			**Person time**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<18 years	84	38	122	108.74	48.51	157.26
18 to <65 years	124	133	257	149.19	159.48	308.67
65 to <75 years	16	11	27	32.19	19.91	52.10
75 or more years	6	2	8	4.43	5.98	10.40
Total	**230**	**184**	**414**	**294.55**	**233.88**	**528.43**

*The data cut-off used for this table was 31-May-2023.
Indication: Cumulative - Studies 160602, 160603, 160902, 161001 (Healthy Volunteers), 161101, 161503, 161504, 170901 - Part 4, 161403, 161505, TAK771-1001 (Healthy Volunteers).

Indication-PID: age/gender groups (person time)*:						
Age group	**Patients**			**Person time (years)**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<18 years	84	38	122	108.74	48.51	157.26
18 to <65 years	64	64	128	65.87	65.21	131.08
65 to <75 years	3	9	12	4.44	12.97	17.41
75 or more years	0	1	1	0.00	3.79	3.79
Total	**151**	**112**	**263**	**179.06**	**130.49**	**309.55**

*The data cut-off used for this table was 31-May-2023.
PID = Primary immune deficiency.
Indication: PID - Studies 160602, 160603, 160902, 161001 (Healthy Volunteers), 161101, 161503, 161504, 170901 - Part 4.

Indication-CIDP: age/gender groups (person time)*:						
Age group	**Patients**			**Person time (years)**		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
<18 years	0	0	0	0.00	0.00	0.00
18 to <65 years	60	69	129	83.31	94.27	177.59
65 to <75 years	13	2	15	27.75	6.94	34.69
75 or more years	6	1	7	4.43	2.18	6.61
Total	**79**	**72**	**151**	**115.49**	**103.39**	**218.88**

*The data cut-off used for this table was 31-May-2023.
CIDP = Chronic inflammatory demyelinating polyradiculoneuropathy.
Indication: CIDP - Studies 161403, 161505, TAK771-1001 (Healthy Volunteers).

Table SIII.4: Ethnic origin by indication

Cumulative for all indications for Ethnic Origin groups (person time)*:		
Ethnic origin	**Patients**	**Person time (years)**
American Indian or Alaska Native	3	6.10
Asian	3	4.39

[redacted]

[redacted]

Cumulative for all indications for Ethnic Origin groups (person time)*:		
Ethnic origin	**Patients**	**Person time (years)**
Black or African American	47	17.92
White/Caucasian	352	482.69
Multiple	4	9.33
Other	1	1.27
Not reported	4	6.74
Total	**414**	**528.43**

*The data cut-off used for this table was 31-May-2023.
Indication: Cumulative - Studies 160602, 160603, 160902, 161001 (Healthy Volunteers), 161101, 161503, 161504, 170901 - Part 4, 161403, 161505, TAK771-1001 (Healthy Volunteers).

Indication- PID: Ethnic Origin groups (person time)*:		
Ethnic origin	**Patients**	**Person time (years)**
American Indian or Alaska Native	2	3.17
Asian	3	4.39
Black or African American	30	11.67
White/Caucasian	223	282.34
Multiple	3	5.58
Other	1	1.27
Not Reported	1	1.13
Total	**263**	**309.55**

*The data cut-off used for this table was 31-May-2023.
PID = Primary immune deficiency.
Indication: PID - Studies 160602, 160603, 160902, 161001 (Healthy Volunteers), 161101, 161503, 161504, 170901 - Part 4.

Indication- CIDP: Ethnic Origin groups (person time)*:		
Ethnic origin	**Patients**	**Person time (years)**
American Indian or Alaska Native	1	2.93
Asian	0	0.00
Black or African American	17	6.25
White/Caucasian	129	200.35
Multiple	1	3.75
Other	0	0.00
Not Reported	3	5.60
Total	**151**	**218.88**

*The data cut-off used for this table was 31-May-2023.
CIDP = Chronic inflammatory demyelinating polyradiculoneuropathy.
Indication: CIDP - Studies 161403, 161505, TAK771-1001 (Healthy Volunteers).

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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 enrolment 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.

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.		It 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; 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 oedema, 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 enrolment	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 is increased 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.
Subjects with abnormal protein loss	It is impossible to do proper PK	No	Physicians must perform a baseline assessment of all

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
(e.g., protein losing enteropathy, nephrotic syndrome, or severe lung disease)	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.		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.	Yes	-
Subjects who had been exposed to any blood product other than an IGIV, SC immunoglobulin, ISG preparations, or albumin within the 6 months prior to	There are certain risks common to administration of any blood- or plasma-derived medicinal product; notably, transfer of infectious agents, renal complications,	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 the benefit-risk balance for each individual prior to prescribing.

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
study entry	haemolysis, 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.		
Subjects who received antibiotic therapy for the treatment of infection within 7 days prior to enrolment or who were receiving prophylactic antibiotic therapy at the time of enrolment 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 enrolment	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) values, calculated	IGIV therapy has been associated with rare cases of renal dysfunction/renal failure and increases in serum creatinine levels. Inclusion of subjects with	Yes	-

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
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))]	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 safe product	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.

[redacted]

Exclusion criterion	Reason for exclusion	Included as missing information	Rationale
administration	administration across the entire trial population.		
Subjects positive at enrolment 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 177 subjects have been exposed to HyQvia in clinical trials: 36 subjects less than 18 years of age, 128 subjects between the ages of 18 and 65 years, and 13 subjects over the age of 65 years.	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 <1/177 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, 18 subjects have been exposed to HyQvia for a period of 1 to <2 years, 21 subjects for a period of 2 to < 3 years, and 30 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 study (PASS) 161302 and 161406.

[redacted]

[redacted]

Ability to Detect Adverse Reactions (AR)	Limitation of Trial Program	Discussion of Implications for Target Population
Due to cumulative effects	In clinical trials, 23 subjects have received > 10 to 30 infusions of HyQvia; 50 subjects have received more than 30 infusions.	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 PASS studies study 161302 and study 161406, study 161504 and phase 3 study 161503.
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 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
Breast-feeding women	

[redacted]

Type of special population	Exposure
	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 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 (as described in section Clinical efficacy and safety). 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.
Elderly	There are limited clinical data in geriatric patients over the age of 65 years; this age group was represented by a total of 13 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 origin	Clinical studies with HyQvia did not exclude subjects based on race or ethnic origin; however, the

Type of special population	Exposure
	majority (132) of participating subjects were Caucasian, with 3 Asian subjects, 28 Black, 12 Hispanic, and 2 of other ethnicities/racial origins. 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.

[redacted]

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 I-IV 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, Baxalta 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 as well as patient exposure for the reporting interval:

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

SV.1.2. Exposure

Based on the above methodology, cumulative global patient exposure since the international birth date is estimated to be approximately 25,899,573 g corresponding to approximately 5,396 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-2023)*

	Cumulative
Units distributed (grams)	25,899,573
Estimated number of patients exposed per month	5,396

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

[redacted]

[redacted]

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.

[redacted]

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.

[redacted]

[redacted]

Important Identified Risks	Risk-benefit impact
AMS	Aseptic meningitis syndrome has been reported 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 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.

[redacted]

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 potential for long-term local and systemic reactions related to potential antibody development against 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

Not applicable.

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.

[redacted]

Important Identified Risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	
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 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

[redacted]

[redacted]

Important Identified Risk: Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency	
	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]. 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).
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-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

Important Identified Risk: **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**	
Potential mechanisms:	Antibodies in immune globulin preparations may interfere with patient responses to live vaccines, such as those for measles, mumps, rubella, and varicella. After infusion of immunoglobulin, the transitory rise of the various passively transferred

[redacted]

[redacted]

Important Identified Risk: **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**	
	antibodies in the patient's blood may result in misleading positive results in serological testing, e.g., hepatitis A virus (HAV), HBV, measles, and varicella. Passive transmission of antibodies to erythrocyte antigens, e.g., A, B, and D, may interfere with some serological tests for red cell antibodies, such as the antiglobulin test (direct antiglobulin test, direct Coombs test).
Evidence source(s) and strength of evidence:	Medical literature
Characterisation of the risk:	Frequency with 95% Confidence Interval Unknown. Seriousness/Outcomes May result in reduced live vaccine efficacy, which could lead to a serious medical condition if the patient contracted the disease for which a vaccination failed. A false positive serologic test could lead to unnecessary additional testing and psychological stress. Severity and nature of risk The severity is variable and depends on the degree of decreased vaccine efficacy. A poorly effective vaccine could still minimise the effects of an infection, but severity would depend on the nature of the infection and resultant disease. The interference with serological test results or false positive results could lead to misdiagnosis and inappropriate treatment. Background incidence/prevalence Given the fact that no current vaccine is 100% effective, even in the ideal circumstances of clinical trials, primary vaccine failure rates have been estimated to range from 2% to 50% for licensed products [redacted]. Recently, a case-control study was conducted to determine whether IGIV exposure was associated with anti-HBc seropositivity in patients with ITP screened for possible inclusion in a randomised trial [redacted]. The study results indicated that recent IGIV exposure was associated with anti-HBc seropositivity, and that approximately 70% (7 of 10) of seropositive patients showed evidence of passive antibody transfer, since they subsequently seroconverted on repeat testing, thus leading to the conclusion that passive transfer of anti-HBc from certain IGIV

[redacted]

[redacted]

Important Identified Risk: **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**	
	products may lead to misinterpretation of hepatitis test results[redacted]. Impact on individual patient Testing of the vaccine-specific antibody titre following vaccination of patients who received HyQvia in temporal association with vaccination may help to confirm the vaccination status. Providers' awareness of the passive transfer of antibodies will prevent incorrect interpretation of laboratory results.
Risk factors and risk groups:	All patients who receive immunoglobulin therapy are potentially at risk for altered immune responses.
Preventability:	Adhere to vaccination schemes and recommendations; re-test in cases of positive serologies. Delay administration of a live attenuated virus vaccine if HyQvia has been administered. Testing of the vaccine-specific antibody titre following vaccination of patients who did receive IGIV in temporal association with the vaccination may help to confirm the vaccination status. Awareness of the passive transfer of antibodies will prevent incorrect interpretation of laboratory results.
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:	In the event of reduced vaccine efficacy, the potential exists for transmission of infectious agents; the actual impact would depend on the nature of the agent.

Important Identified Risk: Infusion site reactions (infusion site leaking)	
Potential mechanisms:	Local tissue inflammation/irritation resulting from leaking of the medicinal product through the skin during physical infusion of the product. 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

[redacted]

[redacted]

Important Identified Risk: Infusion site reactions (infusion site leaking)	
	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]

[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

[redacted]

[redacted]

Important Identified Risk: Thromboembolic events (TEEs)	
	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. • 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 Identified Risk: Haemolysis/Haemolytic anaemia	
Potential mechanisms:	Immunoglobulin products can contain blood group antibodies that may act as haemolysis and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction and, rarely, haemolysis[redacted].
Evidence source(s) and strength of evidence:	SmPC, CCSI, medical literature, post-marketing reports.
Characterisation of the risk:	Frequency with 95% Confidence Interval Unknown; haemolysis has been reported in association with other IV and SC administered immunoglobulin products. Seriousness/Outcomes The outcome and seriousness vary widely and depend greatly on the timing of the diagnosis,

[redacted]

Important Identified Risk: Haemolysis/Haemolytic anaemia	
	initiation of treatment, and discontinuation of IG therapy. Severity and nature of risk May result in a serious medical condition. Background incidence/prevalence A study was conducted to evaluate the relationship between IGIV use and development of haemolytic anaemia and prospective surveillance found that approximately 2.6% of the patients evaluated developed haemolytic anaemia [redacted]. In a more recent study, 1.6% of patients (16 per 1 000) receiving IGIV were identified as haemolysis cases [redacted]. Haemolytic anaemia represents approximately 5% of all anaemias. Impact on individual patient In the case of a severe haemolytic event, patients may experience disability or life-threating/fatal outcomes requiring inpatient hospital care or long-term treatment.
Risk factors and risk groups:	Patients with blood groups A, B, or AB receiving immune globulin therapy are potentially at risk.
Preventability:	Patients who are administered immunoglobulin products should be monitored for signs and symptoms of haemolysis. Patients should strictly adhere to the recommended rate of administration in the SmPC and PL.
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 Identified Risk: Aseptic meningitis syndrome (AMS)	
Potential mechanisms:	The aetiology of aseptic meningitis in patients receiving IGIV is unknown. Proposed causes include the IgG itself, stabilising products, cytokine release triggered by the therapy, cerebrovascular sensitivity in migraineurs IgG dimers/aggregates, and complement activation [redacted].
Evidence source(s) and strength of evidence:	SmPC, CCSI, medical literature, post-marketing reports.
Characterisation of the risk:	Frequency with 95% Confidence Interval Unknown. Seriousness/Outcomes

[redacted]

[redacted]

Important Identified Risk: Aseptic meningitis syndrome (AMS)	
	Symptoms usually resolve after discontinuation of the product but may require hospitalisation. <u>Severity and nature of risk</u> May result in a serious medical condition. <u>Background incidence/prevalence</u> There is a recognised relationship between IGIV and aseptic meningitis[redacted]; however, there is a spectrum of symptoms ranging from acute headache[redacted] to frank aseptic meningitis [redacted] and there have been various estimates of the incidence of drug-induced aseptic meningitis [redacted]. Even so, general drug- and chemical-induced aseptic meningitis is thought to occur rarely[redacted], with reported rates of up to 11% in specific patient groups [redacted]. <u>Impact on individual patient</u> AMS may result in the following acute symptoms which usually begin within several hours to 2days following immunoglobulin treatment and may require intervention. Patients should be informed about first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting.
<u>Risk factors and risk groups:</u>	Aseptic meningitis syndrome has been reported to occur in association with IV and SC immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following immunoglobulin treatment. Patients should be informed about first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting. Discontinuation of immunoglobulin treatment may result in remission of 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.
<u>Preventability:</u>	Since the mechanism is unknown at this time, there are no means to prevent occurrence of aseptic meningitis.
<u>Impact on the risk-benefit balance of the product:</u>	There is currently no impact of this risk on the risk-benefit balance of the product, as the pharmacovigilance and risk minimisation

[redacted]

[redacted]

Important Identified Risk: Aseptic meningitis syndrome (AMS)	
	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: Transmissible infectious agents	
Potential mechanisms:	Viral contamination of medicinal source material of human biologic origin.
Evidence source(s) and strength of evidence:	Medical literature
Characterisation of the risk:	Frequency with 95% Confidence Interval Unknown. Seriousness/Outcomes Event seriousness and outcome would depend on the type and nature of the transmitted infectious agent. Severity and nature of risk The protective measures taken for HyQvia are considered effective for enveloped viruses such as HIV, HBV, HCV, and for the non-enveloped HAV and Parvovirus B19; however, the potential risk for transmission of infectious agents cannot be totally excluded for any blood- or plasma-derived medicinal product. Background incidence/prevalence The risk of contamination by infectious agents is a potential complication to all biological products whose production involves the use of human or animal material. Due to the involvement of these materials, there may be a risk of transmitting infectious agents such as Creutzfeldt-Jakob Disease (CJD) and viruses such hepatitis virus and HIV. The frequency of potential infectious agents in the general population is described below: The CJD is a rare, degenerative, invariably fatal brain disorder. It occurs at a similar rate around the globe, affecting about one person in every one million people per year [redacted]. The HIV/AIDS epidemic affects an estimated 34 million (31.4 million to 35.9 million) people, with an estimated 0.8% of adults aged 15-49 years worldwide living with HIV[redacted]. In Europe, the incidence of HIV cases in 2011 was 7.6 per 100,000, which has remained stable over time. The burden of HBV and HCV varies worldwide. Globally, the prevalence of HBV ranges from 0.2% to 20% and HCV affects approximately 3% of the population[redacted]. In the European region, approximately 14 million people are

[redacted]

[redacted]

Important potential risks: Transmissible infectious agents	
	chronically infected with HBV[redacted]. Overall, the transmission risk of infectious agents from donated blood products has decreased by 3 to 4 orders of magnitude over the past thirty years [redacted]. Impact on individual patient Depending on the nature of the infectious agent and the severity of the event, patients may require inpatient hospital care.
Risk factors and risk groups:	Any patient who is administered a blood- or plasma-derived medicinal product is potentially at risk for transmission of infectious agents.
Preventability:	Screening of plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. The measures taken are considered effective for enveloped viruses such as HIV, HBV, HCV, and for the non-enveloped viruses HAV and Parvovirus B19.
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 nature and transmission pathway of the infectious agent, the potential for widespread transmission cannot be excluded.

Important potential risks: Spread of localised infection	
Potential mechanisms:	Infusion of HyQvia directly into an area of localised infection or acute inflammation may result in the spread of the existing localised infection
Evidence source(s) and strength of evidence:	Medical literature
Characterisation of the risk:	Frequency with 95% Confidence Interval Unknown. Seriousness/Outcomes Event seriousness and outcome would be dependent on the nature of the existing localised infection. Severity and nature of risk Severity would depend on the nature of the existing localised infection. The spread of a localised infection may result in development of a systemic infection. Background incidence/prevalence

[redacted]

Important potential risks: Spread of localised infection	
	The rate at which localised infections spread in the target population is not known at this time. Impact on individual patient The spread of a localised infection may result in development of a systemic infection.
Risk factors and risk groups:	Patients with existing localised infections or acute inflammation who receive SC infusion are at risk for the spread of localised infection.
Preventability:	Strict adherence to the guidelines for administration, i.e., avoiding infusion of HyQvia at or around an area of infection or acute inflammation, as detailed in the SmPC and PL, may minimise this 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:	None

Important potential risks: Renal dysfunction/failure	
Potential mechanisms:	Increased oncotic pressure is one of the postulated mechanisms for acute renal failure following IV immunoglobulin administration [redacted].
Evidence source(s) and strength of evidence:	SmPC, CCSI, medical literature, post-marketing reports.
Characterisation of the risk:	Frequency with 95% Confidence Interval Unknown. Seriousness/Outcomes May result in a seriousness medical condition and/or dependence on long-term dialysis or may potentially lead to a fatal outcome. Severity and nature of risk Renal dysfunction may sometimes be acute in nature and resolve with intermediate treatment and discontinuation of immunoglobulin therapy. Permanent renal failure may require renal dialysis and may potentially be life-threatening or fatal. Background incidence/prevalence Acute renal failure is a rare complication of the use of IGIV, with an estimated incidence lower than 1% [redacted]. Even so, the use of IGIV products, particularly those containing sucrose, has been reported to be associated with a disproportionate occurrence of renal dysfunction, acute renal failure, osmotic

[redacted]

[redacted]

Important potential risks: Renal dysfunction/failure	
	nephropathy, and death[redacted]. However, HyQvia does not contain sucrose. Patients at risk of acute renal failure include those with any degree of pre-existing renal insufficiency, diabetes mellitus, advanced age (> 65 years), volume depletion, sepsis, or paraproteinemia, or those receiving known nephrotoxic drugs. Analysis of reports involving 52 patients experiencing renal failure after administration of IGIV indicated that 58% had pre-existing renal insufficiency[redacted]. <u>Impact on individual patient</u> Depending on the clinical picture, patients may suffer from permanent renal impairment/failure and require renal dialysis.
<u>Risk factors and risk groups:</u>	Cases of acute renal failure have been reported in patients receiving IV administered immunoglobulins, and in most cases, other risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant use of nephrotoxic medicinal products, or age over 65 years.
<u>Preventability:</u>	Patients should not be volume depleted prior to administration of immunoglobulins. Strict adherence to the rate and method of administration outlined in the SmPC and PIL should be practiced.
<u>Impact on the risk-benefit balance of the product:</u>	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.
<u>Public health impact:</u>	Patients may require costly inpatient or long-term outpatient medical treatment.

Important potential risks: Drug administration error: incorrect sequence of administration of products	
<u>Potential mechanisms:</u>	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.
<u>Evidence source(s) and strength of evidence:</u>	Theoretical risk
<u>Characterisation of the risk:</u>	<u>Frequency with 95% Confidence Interval</u> Unknown.

[redacted]

[redacted]

Important potential risks: Drug administration error: incorrect sequence of administration of products	
	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 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 a 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

[redacted]

[redacted]

Important potential risks: Drug administration error: incorrect sequence of administration of products	
	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 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 clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20	
Evidence source:	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. **Population in need of further characterisation:** Long terms use of HyQvia in patient to determine the local and systemic reactions related to potential antibody development against rHuPH20.

[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	
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) 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. **Population in need of further characterisation:** Use in neonates or infants <2 years old. Further characterisation on the effect of prolonged use in patients under the age of 18 years.

[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.
	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.
	Infusion site reactions (infusion site leaking).
	Thromboembolic events (TEEs).
	Haemolysis/Haemolytic anaemia.
	Aseptic meningitis syndrome (AMS).
Important potential risks	Transmissible infectious agents.
	Spread of localised infection.
	Renal dysfunction/failure.
	Drug administration error: incorrect sequence of administration of products.
Missing information	Limited information on safety in pregnant and lactating women.
	Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years.
	Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20.

[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 Allergic/hypersensitivity responses including anaphylactic reactions, especially in patients with IgA deficiency and missing information (Limited clinical data on the influence of the type of PID 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.				

[redacted]

Part IV: Plans for post-authorisation efficacy studies

Not applicable.

[redacted]

[redacted]

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: 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	**Routine risk communication:** SmPC Section 4.4 SmPC Section 4.5 PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The following recommendation provided under SmPC section 4.4 and PL section 2: To inform the doctor about the treatment with HyQvia before any blood test. To wait for up to 3 months before receiving certain vaccines. **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

[redacted]

[redacted]

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 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 **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 identified risks: Haemolysis/Haemolytic anaemia	**Routine risk communication:** SmPC Section 4.4 SmPC Section 4.8 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The following recommendation provided under SmPC section 4.4: Patients should be monitored for clinical signs and symptoms of haemolysis. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Important identified risks: Aseptic meningitis syndrome (AMS)	**Routine risk communication:** SmPC Section 4.4 SmPC Section 4.8 PL Section 4

[redacted]

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: AMS symptoms usually begin within several hours to 2 days following immunoglobulin treatment. Patients should be informed about first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting. Discontinuation of immunoglobulin treatment may result in remission of AMS within several days without sequelae. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Important potential risks: Transmissible infectious agents	**Routine risk communication:** SmPC Section 4.4 PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The following recommendation provided under SmPC section 4.4: Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Important potential risks: Spread of localised infection	**Routine risk communication:** SmPC Section 4.2 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.
Important potential risks: Renal dysfunction/failure	**Routine risk communication:** SmPC Section 4.4 SmPC Section 4.8 PL Section 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** None proposed.
Important potential risks: Drug administration error -	**Routine risk communication:** SmPC Section 2

Safety concern	Routine risk minimisation activities
incorrect sequence of administration of products	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 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 potential for long-term local and systemic reactions related to potential antibody development against rHuPH20	**Routine risk communication:** SmPC Section 4.4 SmPC Section 4.8 PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None.

[redacted]

Safety concern	Routine risk minimisation activities
	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 marketing authorisation holder (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 healthcare professionals (HCP) **Guide for Healthcare Professionals (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.

[redacted]

[redacted]

	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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Immunological Event Questionnaire.

[redacted]

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	reactions and monitor the patients throughout the infusion period. SmPC Section 4.8 PL Section 2 **Additional risk minimisation measures:** None.	**Additional pharmacovigilance activities:** None
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	**Routine risk minimisation measures:** SmPC Section 4.4 and PL section 2 where advice is given wait for up to 3 months before receiving certain vaccines and inform the doctor about the treatment with HyQvia before any blood test. SmPC Section 4.5 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **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 PL Section 4 **Additional risk minimisation measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Expedited reporting of all TEEs. TEE questionnaire. **Additional pharmacovigilance activities:** None.

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	None.	
Important identified risks: Haemolysis/Haemolytic anaemia	**Routine risk minimisation measures:** SmPC Section 4.4 advice to monitor the patients for clinical signs and symptoms of haemolysis. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important identified risks: Aseptic meningitis syndrome (AMS)	**Routine risk minimisation measures:** SmPC Section 4.4 mention that AMS symptoms usually begin within several hours to 2 days following immunoglobulin treatment. Patients should be informed about first symptoms AMS. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important potential risks: Transmissible infectious agents	**Routine risk minimisation measures:** SmPC Section 4.4 contains the standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. PL Section 2 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important potential risks: Spread of localised infection	**Routine risk minimisation measures:** SmPC Section 4.2 PL Section 2 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks: Renal dysfunction/failure	**Routine risk minimisation measures:** SmPC Section 4.4 SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** None.
Important potential risks: Drug administration error - incorrect sequence of administration of products	**Routine risk minimisation measures:** SmPC Section 2 SmPC Section 4.2 contains the recommended infusion rate. SmPC Section 4.4 where advice is given on monitoring and management of adverse reaction. PL Section 3 PL Section 6 **Additional risk minimisation measures:** Educational materials 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 potential for long-	**Routine risk minimisation measures:** SmPC Section 4.4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal**

[redacted]

Safety concern	Risk minimisation measures	Pharmacovigilance activities
term local and systemic reactions related to potential antibody development against rHuPH20	SmPC Section 4.8 PL Section 2 **Additional risk minimisation measures:** None.	**detection:** Immunological Event Questionnaire. **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):

- Primary immunodeficiency syndromes with impaired antibody production
- Secondary immunodeficiencies in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (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.

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 EPAR, including in its plain-language summary, available on the European Medicines Agency (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 analysed, including 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.

[redacted]

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.
	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.
	Infusion site reactions (infusion site leaking).
	Thromboembolic events (TEEs).
	Haemolysis/Haemolytic anaemia.
	Aseptic meningitis syndrome (AMS).
Important potential risks	Transmissible infectious agents.
	Spread of localised infection.
	Renal dysfunction/failure.
	Drug administration error: incorrect sequence of administration of products.
Missing information	Limited information on safety in pregnant and lactating women.
	Limited information on safety in neonates or infants <2 years old and on long-term treatment in patients under the age of 18 years.
	Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20.

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

[redacted]

[redacted]

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

Important Identified Risk: **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**	
Evidence for linking the risk to the medicine	Medical literature
Risk factors and risk groups	All patients who receive immunoglobulin therapy are potentially at risk for altered immune responses.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 and PL section 2 where advice is given wait for up to 3 months before receiving certain vaccines and inform the doctor about the treatment with HyQvia before any blood test. SmPC Section 4.5 **Additional risk minimisation measures:** None.
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

[redacted]

[redacted]

Important Identified Risk: Infusion site reactions (infusion site leaking)	
	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 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Important Identified Risk: Haemolysis/Haemolytic anaemia	
Evidence for linking the risk to the medicine	SmPC, CCSI, medical literature, post-marketing reports
Risk factors and risk groups	Patients with blood groups A, B, or AB receiving immune globulin therapy are potentially at risk.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 advice to monitor the patients for clinical signs

[redacted]

[redacted]

Important Identified Risk: Haemolysis/Haemolytic anaemia	
	and symptoms of haemolysis. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Important Identified Risk: Aseptic meningitis syndrome (AMS)	
Evidence for linking the risk to the medicine	SmPC, CCSI, medical literature, post-marketing reports
Risk factors and risk groups	Aseptic meningitis syndrome has been reported to occur in association with IV and SC immunoglobulin treatment; the symptoms usually begin within several hours to 2 days following immunoglobulin treatment. Patients should be informed about first symptoms which encompass severe headache, neck stiffness, drowsiness, fever, photophobia, nausea, and vomiting. Discontinuation of immunoglobulin treatment may result in remission of 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.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 mention that AMS symptoms usually begin within several hours to 2 days following immunoglobulin treatment. Patients should be informed about first symptoms AMS. SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Important Potential Risk: Transmissible infectious agents	
Evidence for linking the risk to the medicine	Medical literature
Risk factors and risk groups	Any patient who is administered a blood- or plasma-derived medicinal product is potentially at risk for transmission of infectious agents.

[redacted]

[redacted]

Important Potential Risk: Transmissible infectious agents	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 contains the standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. PL Section 2 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Important Potential Risk: Spread of localised infection	
Evidence for linking the risk to the medicine	Medical literature
Risk factors and risk groups	Patients with existing localised infections or acute inflammation who receive SC infusion are at risk for the spread of localised infection.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.2 PL Section 2 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

Important Potential Risk: Renal dysfunction/failure	
Evidence for linking the risk to the medicine	SmPC, CCSI, medical literature, post-marketing reports
Risk factors and risk groups	Cases of acute renal failure have been reported in patients receiving IV administered immunoglobulins, and in most cases, other risk factors have been identified, such as pre-existing renal insufficiency, diabetes mellitus, hypovolemia, overweight, concomitant use of nephrotoxic medicinal products, or age over 65 years.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 SmPC Section 4.8 PL Section 4 **Additional risk minimisation measures:** None.
Additional pharmacovigilance activities	None.

[redacted]

[redacted]

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

[redacted]

[redacted]

Missing information: Limited clinical data on the potential for long-term local and systemic reactions related to potential antibody development against rHuPH20	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 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.

[redacted]

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?
			☐
			☐
			☐
			☐
			☐

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]

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
			☐
			☐
			☐
			☐
			☐
			☐
			☐

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:	

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

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]

[redacted]

[redacted]

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

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 healthcare professionals (HCP)

Guide for Healthcare Professionals (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 (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
- 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)

[redacted]

- 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