[redacted]

EU RISK MANAGEMENT PLAN (RMP)

for

TAK-880 (Human Normal Immunoglobulin)

RMP Version number: 0.4

Date: 13-February-2025

[redacted]

EU Risk Management Plan for TAK-880 (Human Normal Immunoglobulin)

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 0.4

Data lock point for this RMP: 31-December-2023

Date of final sign off: 13-February-2025

Rationale for submitting an updated RMP: The RMP is being updated based on Preliminary Rapporteur's assessment report. As recommended by European Medicines Agency (EMA), the important identified risk of 'Renal failure' has been removed from the list of safety concerns along with the associated targeted questionnaire (TQ) for the safety concern.

Summary of significant changes in this RMP:

RMP Module:	Significant Changes:
Part I Product Overview	Not applicable
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**	Not applicable
• **Module SIV Populations not studied in clinical trials**	Not applicable
• **Module SV Post-authorisation experience**	Not applicable
• **Module SVI Additional European Union (EU) requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	SVII.1.2: Updated to only list safety concerns agreed on with the EMA to be included during the initial marketing authorisation application process. SVII.2: Updated to remove the justification for the removal of safety concerns. SVII.3: Updated to remove the important identified risk of 'Renal failure'.
• **Module SVIII Summary of the safety concerns**	Updated to remove the important identified risk of 'Renal failure' from the list of safety concerns.
Part III Pharmacovigilance plan	Updated to remove the TQ applicable for the risk of 'Renal failure' following removal of the risk.
Part IV Plans for post-authorisation efficacy studies	Not applicable
Part V Risk minimisation measures	Updated parts V.1 and V.3 to reflect the changes in the list of safety concerns in alignment with Part II Module SVIII.
Part VI Summary of the risk management	Updated Parts VI II.A and VI II.B to reflect the

[redacted]

RMP Module:	Significant Changes:
plan	changes in the list of safety concerns.
Part VII Annexes	Annex 4: Updated to remove the 'Renal failure' TQ. Annex 8: Updated summary of changes to the risk management plan over time. All other applicable sections of the RMP have been updated as per the EU RMP template guidance.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP: None

Version number: Not applicable

Approved with procedure: Not applicable

Date of approval (opinion date): Not applicable

Qualified Person for Pharmacovigilance (QPPV) name: Jean-Marie Heim, MD

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

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

[redacted]

Table of contents

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

List of Abbreviations

Abbreviation	Definition/Description
AIDS	Acquired Immune Deficiency Syndrome
AIHA	Autoimmune Hemolytic Anemia
aRMMs	Additional Risk Minimization Measures
AMS	Aseptic Meningitis Syndrome
CAA	Coronary Artery Aneurysms
CAD	Coronary Artery Disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CIDP	Chronic Inflammatory Demyelinating Polyradiculoneuropathy
CJD	Creutzfeld-Jakob Disease
CLL	Chronic Lymphocytic Leukemia
CVA	Cerebrovascular Accident
DVT	Deep Vein Thrombosis
EMA	European Medicines Agency
ESID	European Society for Immunodeficiencies
EU	European Union
g	Gram
GBS	Guillain-Barré Syndrome
GVP	Good Pharmacovigilance Practices
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HL	Hodgkin Lymphomas
HLA	Human Leukocyte Antigen
HSCT	Haematopoietic Stem Cell Transplantation
ICH	Intracranial Hemorrhage
IG 10%	Immune Globulin Infusion (Human) 10%
IgA	Immunoglobulin A
IgAD	IgA deficiency
IgG	Immunoglobulin G
IGIV 10%	Immune Globulin Intravenous (Human) 10%
ITP	Immune Thrombocytopenia
IV	Intravenous (ly)
IVIg	Immunoglobulin for Intravenous Administration

Abbreviation	Definition/Description
KD	Kawasaki Disease
kg	Kilogram
MedDRA	Medical Dictionary for Regulatory Activities
M	Molar
mg	Milligram
ml	Milliliter
MMN	Multifocal Motor Neuropathy
NHL	Non-Hodgkin Lymphomas
NICHD	National Institute of Child Health and Human Development
NOAEL	No-Observed-Adverse-Effect-Level
EPAR	European Public Assessment Report
PBRER	Periodic Benefit Risk Evaluation Report
PID	Primary Immunodeficiency
PIDD	Primary Immunodeficiency Disease
PIL	Patient Information Leaflet
PSAF	Proven Specific Antibody Failure
QPPV	Qualified Person for Pharmacovigilance
SC	Subcutaneous (ly)
SID	Secondary Immunodeficiencies
SCID	Severe Combined Immunodeficiency
S/D	Solvent/Detergent
SmPC	Summary of Product Characteristics
TEE(s)	Thromboembolic Event(s)
TQ	Targeted Questionnaire
TRALI	Transfusion Related Acute Lung Injury
TVR	Triple Virally Reduced
U	Unit(s)
UK	United Kingdom
US	United States
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) (INN or common name)	Human Normal Immunoglobulin (IVIg)
Pharmacotherapeutic group(s) (ATC Code)	Immune sera and immunoglobulins: immunoglobulins, normal human, for intravascular administration (J06BA02)
Marketing Authorisation Holder	Takeda Manufacturing Austria AG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Deqsiga 100 mg/ml solution for infusion
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Human Normal Immunoglobulin (IVIg)
	Summary of mode of action: Human normal immunoglobulin contains mainly immunoglobulin G (IgG) with a broad spectrum of antibodies against infectious agents. Adequate doses of this medicinal product may restore abnormally low immunoglobulin G levels to the normal range. The mechanism of action in indications other than replacement therapy is not fully elucidated but includes immunomodulatory effects.
	Important information about its composition: Human normal immunoglobulin contains mainly IgG with a broad spectrum of antibodies against infectious agents.
Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for latest submitted SmPC.
Indication(s) in the EEA	Current: TAK-880 is indicated for: -*Replacement therapy in adults, children and adolescents (0 to 18 years) in:* • Primary immunodeficiency syndromes (PID) 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 -*Immunomodulation in adults, children and adolescents (0 to 18 years) in:*

	• Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count. • Guillain Barré syndrome • Kawasaki disease (in conjunction with acetylsalicylic acid). • Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). • Multifocal Motor Neuropathy (MMN)
	Proposed: Not applicable
Dosage in the EEA	Current: The dose and dose regimen are dependent on the indication. The dose may need to be individualised for each patient dependent on the clinical response. Dose based on bodyweight may require adjustment in underweight or overweight patients. The following dose regimens are given as guidance: <u>*Replacement therapy in PID syndromes*</u> The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/l or within the normal reference range for the population age. 3 - 6 months are required after the initiation of therapy for equilibration (steady state IgG levels) to occur. The recommended starting dose is 0.4 - 0.8 g/kg given once, followed by at least 0.2 g/kg given every 3 - 4 weeks. The dose required to achieve a trough level of IgG of 6 g/l is of the order of 0.2-0.8 g/kg/month. The dose interval when steady state has been reached varies from 3 – 4 weeks. <u>*Replacement therapy in secondary immunodeficiencies*</u> The recommended dose is 0.2 - 0.4 g/kg every 3 - 4 weeks. <u>*Immunomodulation in:*</u> *Primary immune thrombocytopenia* There are two alternative treatment schedules: • 0.8 - 1 g/kg given on day one; this dose may be repeated once within 3 days • 0.4 g/kg given daily for 2 – 5 days. The treatment can be repeated if relapse occurs. *Guillain Barré syndrome* 0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse). *Kawasaki Disease* 2.0 g/kg should be administered as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid. *CIDP* Starting dose: 2.0 g/kg divided over 2 - 5 consecutive days. Maintenance doses: 1 g/kg over 1 - 2 consecutive days every 3 weeks. *MMN* Starting dose: 2 g/kg divided over 2 - 5 consecutive days. Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks over 2 - 5 days. *Note: Further details on dosage are available in SmPC.*

[redacted]

	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: 100 mg/ml solution for infusion The solution is clear or slightly opalescent and colourless or pale yellow. Each vial of 50 ml contains: 5 g of human normal immunoglobulin. Each vial of 100 ml contains: 10 g of human normal immunoglobulin.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

[redacted]

Part II: Safety specification

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

In alignment with the Guideline on the Clinical Investigation of Human Normal IVIg on 28-June2018, EMA/CHMP/BPWP/94033/2007 rev. 3 and the Guideline on core SmPC for human normal IVIg, EMA/CHMP/BPWP/94038/2007 rev. 6 , TAK-880 is proposed to be indicated for

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

- Immunomodulation in adults, children and adolescents (0-18 years) in:
  - Primary immune thrombocytopenia (ITP), in patients at high risk of bleeding or prior to surgery to correct the platelet count.
  - Guillain Barré syndrome.
  - Kawasaki disease (in conjunction with acetylsalicylic acid).
  - CIDP.
  - Multifocal Motor Neuropathy (MMN)

Immunoglobulin replacement therapy and immunomodulation Indications:	
Incidence:	***Primary immunodeficiency diseases (PIDD) syndromes*** PID syndromes or diseases (PIDD) are recognized 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 . The International Union of Immunological Societies (IUIS) Expert Committee on Primary Immunodeficiencies currently recognizes more than 354 primary immunodeficiency syndromes that can be caused by defects in 344 distinct genes . There are now a total of 485 inborn errors of immunity . However, some forms of PIDD are extremely rare, so fewer than 20 types comprise more than 90% of all PIDDs. The true frequency of PIDD in the general population, either individually or in aggregate, has not been ascertained, but estimates have been reported. In aggregate, the estimated incidence of diagnosed PIDD has been reported as 1 per 10,000 persons . Prevalence estimates of PIDD, especially in children and adolescents may be understated. A United states (US)-based survey conducted by the National Immune Deficiency Foundation reported that 60% of patients diagnosed with PID were not diagnosed until adulthood despite the occurrence of serious and chronic infections, many resulting in hospitalization. ***Secondary Immunodeficiencies (SID)*** Secondary immunodeficiencies, which are more common than PIDs , result from a variety of factors that can affect a host with an intrinsically normal immune system, including infectious

[redacted]

Immunoglobulin replacement therapy and immunomodulation Indications:	
	agents, drugs, metabolic diseases, and environmental conditions[redacted] SID occurs when the immune system is weakened by another treatment or illness. Hence, SIDs are not genetic in nature, but instead a result of external factors such as chronic illnesses e.g., leukaemias, chronic infections such as human immunodeficiency virus (HIV), extreme age or extreme external factors such as malnutrition, etc. Some examples of SID include the following: *Perinatal AIDS (with recurrent bacterial infections)* Globally, it is estimated that approximately 500 children are infected with HIV each day [redacted]. In 2021, there were an estimated 4.3 per 100,000 population diagnosed with HIV in the EU/EEA. Among those with HIV, <1% of the cases (95 individuals) in the EU were acquired by perinatal transmission[redacted]. Among those HIV positive in the US in 2015, 9,562 persons were known to be living with perinatal HIV[redacted]. There are numerous immunological defects in HIV infected children which cause them to be extremely vulnerable to infections, especially bacterial infections, as compared to individuals without HIV. As the disease progresses, deficits in humoral immunity are thought to be directly related to the high rate of recurrent bacterial infections in those with symptomatic HIV [redacted]. The consequences are severe infections with ubiquitous encapsulated bacteria, which appear before or with viral and other opportunistic infections. In a large observational study the most serious bacterial infections that frequently occurred in children with perinatal HIV were bacterial sepsis (56%) and pneumonia (25%) [redacted]. *Multiple myeloma* The second most common hematologic cancer in the Western world is multiple myeloma, accounting for 10% to 15% of all hematologic malignancies[redacted]. In patients afflicted with multiple myeloma, cancerous plasma cells quickly proliferate and accumulate throughout the body causing bone destruction, anemia, renal damage and increased susceptibility to infection [redacted]. This hematologic cancer affects all ages; however, incidence 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]. Worldwide, incidence ranges from 0.4 to 6 cases per 100,000 person-years, representing 0.8% of all cancer diagnoses[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 leukemia (CLL) with hypogammaglobulinemia* CLL is recognized as the most common leukemia in the Western world accounting for approximately 30% to 40% of all forms of leukemia[redacted]. This form of leukemia, 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 anemia, bleeding, and

[redacted]

[redacted]

Immunoglobulin replacement therapy and immunomodulation Indications:	
	susceptibility to infection [redacted]. Hypogammaglobulinaemia, 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]. 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]. *Allogeneic hematopoietic stem cell transplantation (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. 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]. 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]. *Guillain-Barré syndrome (GBS)* Guillain-Barré syndrome is an autoimmune disease that affects the peripheral nervous system. It is characterized by a symmetric ascending paralysis, hyporeflexia or areflexia. It is a monophasic syndrome with severity peak between two to four weeks after onset. It is the most common cause of acute or subacute flaccid weakness in the world after the eradication of poliomyelitis. In the period of study (1985 – 2019), the GBS incidence rate among the cohort studies in the general population varied from 0.30 in Brazil to 6.08 cases per 100,000 habitants in Martinique. The estimated incidence in the USA was 6.58 cases per 100,000 person-years (CI 95% 5.05-8.24) [redacted]. *Kawasaki Disease (KD)* Kawasaki disease primarily is a rare condition that predominately impacts children under the age of 5 and the incidence varies by region[redacted]. The incidence of KD in children

[redacted]

Immunoglobulin replacement therapy and immunomodulation Indications:	
	in Europe ranges from 1.6 per 100,000 in the Czech Republic to 17.6 per 100,000 in Italy. Furthermore, the prevalence is 11.4 per 100,000 in Finland, 7.4 per 100,000 in Sweden, 5.4 per 100,000 in Norway, 4.9 per 100,000 in Denmark, 9.1 per 100,000 in the UK, 15.2 per 100,000 in Ireland, 9 per 100,000 in France, 6.5 per 100,000 in Portugal, 11.7 per 100,000 in Spain, 9.6 per 100,000 in Germany, 5.8 per 100,000 in the Netherlands, and 9.6 per 100,000 in Estonia [redacted]. *Multifocal Motor Neuropathy (MMN)* MMN is a rare condition with a prevalence of less than 1 per 100,000 [redacted]. *Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)* CIDP is a rare, immune-mediated disorder in which an aberrant immune response causes demyelination and axonal damage of the peripheral nerves. Symptoms of CIDP include progressive weakness, impaired sensory function in the legs and arms, loss of deep tendon reflexes (areflexia), and fatigue. CIDP is a long-term condition with a course that can be relapsing-remitting, stepwise progressive, or gradually progressive[redacted]. Global incidence for CIDP was estimated by Broers et al. the meta-analysis (n= 5 studies) included 818 cases based on EFNS/PNS 2006 criteria and 220,513,514 person-years of observation. Crude incidence rates varied between 0.15 and 0.70 cases per 100,000 person-years, and the pooled crude incidence rate for the total population is 0.33 per 100,000 person-years (95% CI 0.21-0.53, I2 = 95.7%. The pooled crude incidence rate for studies using the AAN criteria is 0.36 per 100,000 person-years (95% CI 0.30–0.44, I2 = 0.0%; prediction interval 0.30–0.44). Incidence of CIDP was consistently seen more in males than females. The authors note that there was significant heterogeneity between studies which can impact the precision of the estimates [redacted]. Globally, the incidence of CIDP ranges from 0.2 to 1.6 per 100,000 [redacted]. The incidence varies by region, with a reported incidence rate of 0.37 per 100,000 in Italy, 0.25 per 100,000 in Iceland, and 0.7 per 100,000 in the UK [redacted]. A study in Netherlands reported an incidence rate of 0.68 per 100,000 [redacted].
Prevalence:	***Primary immunodeficiency diseases (PID) syndromes*** Recent estimates have suggested that PIDD has far greater prevalence than has been previously suggested in the literature. 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 6.16/100,000 inhabitants in France in 2014 [redacted], 5.6/100,000 in Australia in 2007 [redacted], 3.71/100,000 in the UK in 2014, and 2.14/100,000 in Germany in 2014, and 0.12/100,000 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 US. A US national probability sample conducted in 2005 suggested a population prevalence of diagnosed PID at

Immunoglobulin replacement therapy and immunomodulation Indications:	
	approximately 1 in 1,200 individuals (86.3/100,000 inhabitants), whereas earlier estimates placed the prevalence at 1 in 10,000[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]. By contrast, common variable immunodeficiency (CVID) is the most symptomatic and therefore most frequently diagnosed primary immunodeficiency (PID) in adults, with an incidence of approximately 2 per 100,000 [redacted]. ***Secondary Immunodeficiencies (SID)*** The most prevalent secondary immunodeficiency is the one caused by HIV and causes the acquired immunodeficiency syndrome, which prevalence varies worldwide. There were approximately 38.4 million (33.9 million–43.8 million) people globally were living with HIV in 2021 and 28.7 million people were accessing antiretroviral therapy in 2021 [redacted]. Some examples of SID include the following: <u>*Chronic lymphocytic leukemia (CLL) with hypogammaglobulinemia*</u> 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]. <u>*Allogeneic hematopoietic stem cell transplantation (HSCT)/with hypogammaglobulinemia*</u> 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]. <u>*Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)*</u> The Broers et al meta-analysis of prevalence (n=9 studies) included 3,160 cases based on EFNS/PNS criteria and a population size of 160,765,325. The crude prevalence rate varied between 0.67 and 7.7 cases per 100,000 persons. The pooled crude prevalence rate for the total population is 2.81 per 100,000 (95% CI 1.58–4.39, I2 = 99.1%) The estimated prevalence based on the AAN criteria is 2.52 per 100,000 (95% 1.41–3.95, I2 = 99.0%). The authors report heterogeneity between studies which may affect precision of the estimate. In general, reported crude prevalence rates were higher in males than in females (gender rate ratios varied between 1.4 and 4.4 [redacted]. The prevalence for CIPD varies regionally. Globally, the prevalence ranges from 0.8-10.3 per 100,000[redacted]. In Europe, the prevalence ranges from 2.8 per 100,000 to 7.7 per 100,000. The prevalence rate is approximately 2.8 per 100,000 in England, approximately 5.6 per 100,000 in Ireland,

Immunoglobulin replacement therapy and immunomodulation Indications:	
	and approximately 7.7 per 100,000 in Norway [redacted]. In Netherlands, one study found an overall prevalence rate of 7 per 100,000[redacted]. *Kawasaki Disease (KD)* Kawasaki disease is an acute disease; therefore incidence, described above, is the appropriate metric of the disease in a population. *Multifocal Motor Neuropathy* Worldwide prevalence of MMN is less than 1 per 100,000[redacted]. One study in Austria indicated a prevalence of 0.65 per 100,000 [redacted], while the prevalence in Netherlands is estimated to be 0.5 per 100,000[redacted].
Demographics of the target population in the indication:	***Primary immunodeficiency diseases (PID) syndromes*** Physician-reported patient demographics in 2021 were compared with that of 2018 and 2013. Reports included information on gender for 62,045 patients and on age for 56,187 patients. Of these patients, 58% were male and 42% were female, globally. In the US alone, 56.3% were male, and 43.7% were female. It was reported that 64.2% of these patients were 0–19 years old, and 35.8% were 20+ years old, globally. The demographic distribution has largely remained consistent since 2013 [redacted]. Selective IgA deficiency can occur as frequently as one in 300 people. For individuals who are Caucasian and of European descent, the rate is one in 500 to 700, and for individuals of Japanese descent, it affects only about 1 in 18,500[redacted]. ***Secondary Immunodeficiencies (SID)*** *Multiple myeloma* Among the general population, men are 1.5 times more likely to develop multiple myeloma than women, additionally, genetic predispositions also may increase this risk [redacted]. For example, studies conducted in Iceland and Sweden of multiple myeloma have reported a more than two-fold elevated risk among those who are first degree relatives of patients with multiple myeloma [redacted].
Risk factors for the disease:	PID is a genetic disorder, the only known risk factor for development of PID is family history of the disease. SID onset is the result of acquired declines in immune cell counts or function. Most commonly, SID is due to decreased antibody levels following exposure to extrinsic factors such as an underlying illness or exposure to a medicine to treat an autoimmune disease or hematological malignancy[redacted]. Examples of extrinsic factors for SID include: • Hematological Malignancy: A systematic review of 89 studies that assessed outcomes in chronic lymphocytic leukaemia (CLL), multiple myeloma (MM), and non-Hodgkin lymphoma (NHL) showed high risk for development of SID following oncological treatment. Across CLL, MM, and NHL, 51.3%, 35.9%, and 35.4% of patients experienced infections of any grade, and any grade neutropenia was reported in 36.3%, 36.4%, and 35.4%, respectively. The highest proportion of grade

[redacted]

Immunoglobulin replacement therapy and immunomodulation Indications:	
	≥3 infections was among patients with MM treated with a B-lineage monoclonal antibody combination (41.0%) [redacted]. • Infections: HIV infection targets CD4 T cells leading to T cell lymphopenia through several causes including HIV-induced apoptosis. Diminished CD4 T cells count leave the host susceptible to opportunistic infections. Measles virus can result in immunosuppression lasting from months to years via a proposed mechanism of T and B cell lymphoma. • Immunosuppressive medications: Medicines designed to target cytokines and cells of the immune system include small molecules (e.g., corticosteroids, methotrexate), JAK inhibitors, Monoclonal antibodies that target B cells, IL-1 and IL-6 inhibitors that reduce inflammatory response. • Malnutrition: Direct effects of malnutrition in lymphoid organs have been observed in malnourished mice including decreased levels of secretory IgA. Malnourished individuals have reduced numbers of memory and effector T cells, reduced delayed-type hypersensitivity, impaired T cell responses, and fewer circulating B cells[redacted].
The main existing treatment options:	Treatment regimens with TAK-880 may vary slightly from region to region. In one study [redacted], differences were found in the routine use of immunoglobulin therapy such as initial dosing and dosing intervals, the types of PIDD in that locality, the types of prophylactic antibiotics, the perceived benefit of immune globulin intravenous (IGIV), and reimbursement policies in each region. The following, therefore, is a general overview of the most widely used concomitant medications by indication. *Primary immunodeficiency (PID) syndromes* Characteristic clinical manifestations in patients with PID depend upon the constituent of the immune system that is deficient[redacted]. Although patients with PID and secondary immunodeficiencies are prone to recurrent infections, the number of recurrences has decreased and the infections that do happen tend to be less severe with immunoglobulin therapy. Still, these infections may require the use prophylactic antibiotics as an adjunct therapy and inactivated vaccines[redacted] and/or possibly, anti-inflammatory therapies. Some of the most commonly prescribed prophylactic antibiotics are presented by category in the table below: **Anti-Inflammatory therapies**

Category	**Antibiotic(s)**
Fluoroquinolones	Ciprofloxacin, Gemifloxacin, levofloxacin, moxifloxacin
Penicillin derivatives	Amoxicillin, amoxicillin/clavulanic, penicillin V potassium, ampicillin
Cephalosporins	Cefazolin, cefixime, cefotetan, cefuroxime
Macrolides	Azithromycin, Clarithromycin, Erythromycin

[redacted]

[redacted]

Immunoglobulin replacement therapy and immunomodulation Indications:	
	Sulfonamides | Trimethoprim-Sulfamethoxazole The impaired immune system in patients with PID increases their risk of certain cancers specifically lymphoid malignancies. Non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) are the two most common PID-associated malignancies [redacted]. HL is differentiated by the recognition of the hallmark Sternberg-Reed cells. All other forms of lymphoma fall into the NHL grouping. Chemotherapeutic regimens for both groups will vary according to the disease state and may often be followed by radiotherapy. There are several subtypes of NHL and treatment will vary based on which subtype a patient may have. Cyclophosphamide, hydroxy doxorubicin, vincristine, prednisone (CHOP) is one of the most commonly used chemotherapy regimens for treating NHL[redacted]. CHOP may also be used in conjunction with other immunotherapy drugs such as rituximab which may be abbreviated CHOP-R. The favoured chemotherapy combination for Hodgkin's disease will vary by geographical region [redacted]. In Europe, a combination of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) is the chemotherapeutic regimen of choice. The most frequently used combination of drugs in the US is adriamycin, bleomycin, vinblastine and dacarbazine (ABVD). Side effects from chemotherapy will vary based on the specific agent and may become more severe as the doses increase. Common side effects include nausea, vomiting, diarrhoea, hair loss, weight loss, and depression. More serious side effects may include neutropenia, anaemia, infection, liver/kidney damage, thrombocytopenia, and allergic reactions. Long term complications are contingent upon the cumulative drug dose and rate of administration. Some of the long-term complications include somatic symptoms such as fatigue and general aches and pain; infertility; some women may cease to menstruate; osteoporosis; heart failure (more common with anthracyclines); and compromised pulmonary function particularly with bleomycin. Both autologous and allogenic hematopoietic stem cell transplants (HSCT) offer other therapeutic options; autologous is usually favoured over allogenic. Stem cell transplantation is preceded by a conditioning process which requires high dose chemotherapy and/or radiation to kill unhealthy cells. The most common side effects of chemotherapy are highlighted above. Patients undergoing radiation therapy typically experience skin changes and fatigue. The other side effects depend on the part of the body being treated. *Secondary immunodeficiencies* 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

[redacted]

Immunoglobulin replacement therapy and immunomodulation Indications:	
	may be administered with prednisone to treat nausea and vomiting. A general side effect profile for chemotherapeutic agents is outlined earlier. For patients with CML, drugs known as tyrosine kinase inhibitors (TKIs) that target a specific gene found in CML are the standard treatment[redacted]. These drugs are less likely to affect normal cells, so their side effects are generally not as severe as those seen with other drugs that can be used to treat CML, such as traditional chemotherapy drugs. Besides the haematological side effects of most of TKIs like anaemia, thrombopenia and neutropenia, the most common adverse effects are oedema, nausea, hypothyroidism, vomiting and diarrhoea. More serious and possibly long-term effects include pleural effusion, prolonged QT syndrome, liver damage, and congestive heart failure. Drugs that treat HIV/AIDS known as antiretroviral therapy (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-nucleoside reverse transcriptase inhibitors (NNRTIs) such as efavirenz or nevirapine; protease inhibitors (PIs) like amprenavir or tipranavir; integrase inhibitors (raltegravir and dolutegravir); enfuvirtide (a fusion inhibitor) and/or entry inhibitors such as maraviroc [redacted]. The most common side effects of ART are nausea, vomiting diarrhea, 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 two commonly used regimens [redacted]. Chemotherapy associated adverse reactions can range from mild/moderate such as nausea, vomiting, diarrhea to severe such as liver/kidney damage, thrombocytopenia. Patients undergoing radiation therapy typically experience. AEs associated with radiation therapy are skin changes and fatigue and those that are specific to the part of the body being treated. *Immunomodulation therapies* Symptoms of ITP can range from mild bruising, mucosal bleeding such as oral or gastrointestinal tract to haemorrhage from any site, the most serious of which is intracranial[redacted]. For patients receiving IGIV for ITP there may have concomitant use of corticosteroids to help raise the platelet count and thrombopoietin receptor agonists like romiplostim and eltrombopag to help the bone marrow make more platelets. A biologic like rituximab may also be used. Corticosteroids may cause weight gain, cataracts, high blood sugar, increased risk of infections and osteoporosis. Possible side effects of thrombopoietin receptor agonists include headache, joint or muscle pain, dizziness, nausea or vomiting, and an increased risk of blood clots. Rituximab may cause low blood pressure, fever, sore throat and rash. IGIV is also to treat the autoimmune disorders MMN and GBS.

[redacted]

Immunoglobulin replacement therapy and immunomodulation Indications:	
	Patients with MMN, and autoimmune disorder, experience a slow progression of motor deficits and sensory loss primarily in the upper extremities. Symptoms for some patients are mild and no treatment is required. IGIV is the treatment of choice. Immunosuppressant therapy like cyclophosphamide has been used however, there is concern over its toxicities such as bone marrow suppression, alopecia, hemorrhagics cystitis, delayed bladder cancer, teratogenicity, azoospermia, and infection risk. Rituximab, mycophenolate mofetil, ßinterferon, cyclosporine, azathioprine, and infliximab have been used although controlled trials have not been sufficient to support their use[redacted]. Weakness and tingling in the extremities are usually the first symptoms of GBS. These symptoms may quickly progress and eventually lead to paralysis. These patients experience severe physical disability and often require prophylactic use of subcutaneous (SC) heparin to prevent thrombosis[redacted]. The most commonly occurring adverse effects of SC heparin are injection site bruising, injection site pain, and hematoma. Heparin induced thrombocytopenia (HIT) is a more serious, possibly life-threatening effect is[redacted] associated with high rates of thromboembolic events (TEEs). Data has shown that the risk of HIT increases in patients receiving prophylactic SC heparin for longer than 1 week. Along with IGIV therapy, high-dose aspirin (80–100 mg/kg daily divided into four doses) is the primary treatment in children with Kawasaki syndrome [redacted]. High doses of aspirin are used in the acute inflammatory stage. When inflammatory markers have returned to normal and the patient has been afebrile for 3–7 days, a low-dose (3–5 mg/kg daily) antiplatelet regimen of aspirin is continued. The most common side effects of aspirin are gastrointestinal irritation and abnormal liver function. Aspirin has been linked to Reye's syndrome in children experiencing infection with varicella and influenza. In some cases, children may require anti-thrombotic therapy such as clopidogrel, warfarin, or heparin[redacted]. Any of these antiplatelet agents can cause gastrointestinal disorders such as nausea, vomiting and diarrhea; skin disorders such as rash and pruritus, and hypersensitivity reactions. The chief concern with either of these agents is mild bleeding (hematoma, bruising) to hemorrhage. Additionally, patients receiving IGIV therapy commonly require pre-medication with corticosteroids, antipyretic/anti-inflammatory drugs (e.g., acetaminophen, NSAIDs), and/or antihistamines. Some of the most common side effects of corticosteroids include lower resistance to infection, increase in blood glucose or worsening of diabetes, easy bruising, water retention, gastrointestinal irritation, weight gain and muscle weakness. NSAIDs increase the risk of gastrointestinal bleeding, heart attack, and stroke with COX-2 inhibitors like celecoxib and parecoxib. The more common reactions with antihistamines include dry mouth, dizziness, drowsiness, and fatigue.
Natural history of the indicated condition in the untreated population, including mortality	Outcome and prognostic factors in patients with primary and secondary immunodeficiency may vary by severity, stage of disease and rate of progression. A summary of the reported

[redacted]

Immunoglobulin replacement therapy and immunomodulation Indications:	
and morbidity:	outcomes in the target population are discussed below. *Primary immunodeficiency (PID)syndromes* The prognosis of patients with PID varies depending on the etiology of the disorder, with the major factor in assessing prognosis dependent on the extent of damage to the lungs and other organs as well as how successful future complications can be prevented. Upon examining patients with a spectrum of PID 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 the highest mortality observed in individuals with severe combined immunodeficiencies (13 %) and ataxia-telangiectasia (13 %) [redacted]. Overall, the major cause of mortality was severe infection accounting for 56% (42/75) of deaths in the population[redacted]. *Secondary Immunodeficiencies* 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 multiple myeloma [redacted]. Overall, 5-year age adjusted survival rates for multiple myeloma 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, characterized 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].

Immunoglobulin replacement therapy and immunomodulation Indications:	
	Immunomodulation therapies: In a European population-based study, mortality in adult patients with primary ITP was reported to be approximately 22% at 5 years, which increases to 49% at 20 years post diagnosis[redacted]. Mortality in the afflicted population was 1.5 times higher than the general population, primarily as a result of infection and bleeding. This risk of death was predominately found in patients older than 60 years of age and highest among males. In contrast, patients with GBS have a lower rate of mortality of about 3% [redacted]. Many individuals may suffer with severe pain, which acutely affects 50% to 89% percent of patients. During the acute stage between 3% and 12% of patients die of complications[redacted]. Additionally, patients afflicted by GBS may suffer long term morbidity in the form of neurologic problems that may persist in 20% of patients, with half of these patients becoming severely disabled [redacted]. Overall, most GBS patients recover completely with no lasting symptoms [redacted]. Similarly, KD is generally a self-limiting disease, with most patients recovering without lasting burden [101]. Worldwide, mortality rates of treated patients with KD are low, varying across countries from0.0003% in Japan to 0.04% in Canada[redacted]. Patients with MMN also have low mortality with a normal life expectancy similar to the general population [redacted]. However, MMN patients who survive may suffer with severe morbidity in the form of immobilization and/or severe fatigue which has been reported in 20% and 50% of patients, respectively[redacted].
Important co-morbidities:	***Recurrent infections*** Many patients with PID or a secondary immunodeficiency are susceptible to persistent recurrent infections, which if left untreated, may be fatal. Various patients with PID 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 diarrhea prior to diagnosis. Although far less common, relatively high rates of malabsorption (9%), sepsis (5%), meningitis (4%), and hepatitis (3%) are also reported prior to diagnosis [redacted]. Despite the common occurrence of infections in PID, patient outcomes and long-term survival have improved significantly in recent years (compared to the 1970s), given improved management of infections and early access to antibiotics, advances in bone marrow and hematopoietic stem cell transplantation techniques, and enhanced intensive care services[redacted]. It is also believed that routine vaccinations provide herd immunity to those at risk, thus decreasing the circulation of infectious diseases. Patients with a secondary immunodeficiency, which may be acquired from malignancies or HIV, are also at risk for a spectrum of infections associated with disease complications or related to the immunosuppressive impact of treatment. The risk of infectious complications, in patients with CLL early in disease, is highly associated with hypogammaglobulinemia and increased susceptibility to bacterial infections[redacted]. Recurrent infections, commonly from respiratory and severe urinary tract

Immunoglobulin replacement therapy and immunomodulation Indications:	
	infections, occur in as many as 80% of patients with CLL [redacted]. Similarly, multiple myeloma patients are especially prone to increased incidence of bacterial septicemia and infection of the respiratory and urinary tracts [redacted]. In a population based study conducted in Sweden, patients with multiple myeloma 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), bacteremia (16 per 1,000 person years), and urinary tract infections (33 per 1,000 person years) which become more frequent with increasing immunosuppression [redacted]. ***Autoimmune Conditions*** Autoimmune conditions are a frequent manifestation in some patients with PID, and are often triggered by dysfunction of the innate or adaptive immune response [redacted]. Represented by over 80 heterogeneous conditions, autoimmune conditions are considered rare among the general population, and collectively they affect approximately 3% to 5% percent of the population in Western countries [redacted]. In patients with PID, autoimmunity occurs at a significantly higher incidence commonly appearing as the first presentation of immune deficiency [redacted]. In common variable immunodeficiency (CVID), approximately 25% to 30% of subjects develop autoimmune conditions; and while unclear more than 50% of these involve the hematological system[redacted]. In a recent study, symptoms of autoimmunity were present in 86% of patients either prior to or at the time of CVID diagnosis [redacted]. The most prevalent conditions in these patients were cytopenias in the form of ITP in 43%, autoimmune hemolytic anemia (AIHA) in 26%, and Evans syndrome in 31%. In the general population these conditions are rare, as ITP occurs in only 1 to 12.5 persons per 100,000 population and AIHA is found in 1 to 3 persons per 100,000 population[redacted]. Although the exact frequency of Evans syndrome is unknown, the estimated prevalence of diagnosis is 0.8% to 3.7% in all patients with either ITP or AIHA [redacted]. Cytopenias are also a prevalent manifestation of autoimmunity in 40% to 70% of patients with Wiskott-Aldrich syndrome (WAS) [redacted]. Among WAS patients 25% are often concurrently affected by multiple autoimmune conditions [redacted]. Other PIDD patients are reported to have a spectrum of conditions including but not limited to AIHA, inflammatory bowel disease, and arthritis [redacted]. The heterogeneous manifestations of autoimmunity among PIDD patients may make the diagnosis of this coexistence difficult, thereby impacting therapeutic strategy and clinical outcomes. ***Malignancy*** Malignancies as a clinical complication often arise more frequently in patients with some PIDs [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 PID population, Hodgkin lymphoma (HL) and Non-Hodgkin

Immunoglobulin replacement therapy and immunomodulation Indications:	
	lymphomas (NHL) 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 PID patients[redacted]. This rare neurologic PID, 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 PID population [redacted]. The prevalence of overall cancer in a national patient sample of A-T patients was found to represent an excess of 70 fold for leukemia and was more pronounced for NHL with an excess of 250 fold as compared to the general population [redacted]. Diagnosis of leukemia and NHL in A-T patients primarily occurs in adolescents younger than 10 years of age[redacted]. ***Intracranial hemorrhage*** Intracranial hemorrhage (ICH) is the most severe and often devastating complication of ITP in children and adults. Presentation of ICH primarily occurs within days of acute ITP, with approximately 30% developing in those with chronic ITP[redacted]. In a retrospective study the median time from diagnosis of ITP to ICH was 32 days (range 0 days to 8 years) [redacted]. Seventy-two percent of ICH cases (50/60) occurred within 6 months of diagnosis, but only 10% (7) occurred within 3 days of diagnosis. Globally, ICH occurs with an incidence of 0.1% to 1.0%, predominantly affecting children [redacted]. While injury can be a precipitating factor, ICHs may occur without any history of trauma or predisposing factors [redacted]. Generally, due to the rarity of this complication, clinical indicators, predictors, and outcomes have been difficult to pinpoint. A large US nationwide survey in children with ITP was recently conducted to examine risk factors and outcomes of ICH [redacted]. In this study, ICH was strongly associated with severe thrombocytopenia (75%), head trauma (33%), and history of hematuria (22%)[redacted]. Although ICH occurs in less than 1 in 100 children with ITP, it represents the major cause of death in children (25% to 50%) as compared to adults with ITP [redacted]. Without the complication of ICH 60% to 80% of ITP patients recover within months without clinical consequence[redacted]. ***Inflammatory Coronary Artery Disease (CAD)*** In general, CAD is rare in young people, with a rise in incidence primarily seen later in life. However, Kawasaki disease is the leading cause of acquired CAD in young patients worldwide [redacted]. Unlike other common forms of heart disease, the pathogenesis of CAD primarily is driven by acute vasculitis without involvement of atherosclerosis. As a result of vascular inflammation 15% and 25% of untreated KD patients develop coronary ectasia and coronary artery aneurysms (CAA), respectively[redacted]. CAA present as one of the most serious complications of KD, with an observed incidence of 4% in young patients receiving treatment at a North American Medical Center which is higher than the incidence of 1.5% found in the general population[redacted]. Many patients present with cardiovascular abnormalities early in the course of disease, often during the first few days of KD diagnosis[redacted]. Patients with incomplete or atypical KD are also susceptible to complications, particularly those younger

[redacted]

Immunoglobulin replacement therapy and immunomodulation Indications:	
	than 12 months old [redacted]. Myocardial infarction, which is generally a result of thrombosis in inflamed coronary arteries, is the most common cause of death in patients with KD. Worldwide mortality rates of treated patients with KD are low, varying across countries from 0.0003% in Japan to 0.04% in Canada [redacted]. ***Depression and anxiety (following severe physical disability)*** In patients afflicted with multifocal motor neuropathy, muscles slowly atrophy, leading to a progressive loss of physical function and increased disability in daily activities. Such progressive debilitation may impact a patient's psychological status leading to the development of depression and anxiety. Mood disorders, such as depression and anxiety, have been recognized as key factors in a patient's overall well-being and clinical progress [redacted]. Among patient populations with slow progressive neuromuscular dysfunction studies have found that patients report a prevalence of 11% to 59% for depression and as high as 90% for anxiety[redacted]. Increased psychological distress was found to be associated with patients' anticipatory anxiety of successive loss of physical function [redacted]. This disabling predicament left many patients in a depressive state of feeling hopeless and helpless, which ultimately impacts clinical improvement [redacted]. However due to the rarity of MMN there is scarce literature examining depression and anxiety in this specific population, therefore the exact incidence and prevalence of these disorders in MMN remain unknown.

[redacted]

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

TAK-880 and KIOVIG essentially are comparable. The nonclinical data of KIOVIG can be extrapolated to TAK-880 and the data are presented below. In addition, the studies specifically performed with TAK-880 are presented. Key safety findings from nonclinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Toxicity:	
Single-dose toxicity: *PV0330101* *Determination of Acute Toxicity in Mice after Intravenous Administration of IGIV (Human) 10% Triple Virally Reduced Solution.* Mice were administered a single dose of 2,500, 5,000, or 10,000 mg/kg KIOVIG or GAMMAGARD solvent/detergent (S/D), the highest applicable volume, by the IV route. Behavioral depression with or without dyspnea was observed in the surviving animals of the group treated with 10,000 mg/kg KIOVIG. 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 KIOVIG. *PV0340101* *Determination of Acute Toxicity in Rats after Intravenous Administration of IGIV (Human) 10% Triple Virally Reduced Solution.* Rats were administered a single dose of 2,000 mg/kg KIOVIG 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 KIOVIG.	Acute toxicity studies with KIOVIG (IGIV, 10%) in mice and rats demonstrated no clinical findings or histopathological changes related to treatment with KIOVIG (IGIV, 10%) up to a NOAEL of 5,000 mg/kg and 2,000 mg/kg for mice and rats, respectively and suggested that KIOVIG (IGIV, 10%) is safe at these doses.
Repeat-dose toxicity No studies on repeat-dose toxicity were performed	Not applicable
Reproductive/ Developmental toxicity No studies on reproductive or developmental toxicity were performed	Not applicable
Genototoxicity: *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.	KIOVIG (IGIV, 10%) is not considered to have genotoxic potential.
Carcinogenicity: No studies on carcinogenicity were performed.	Not applicable
Other toxicity-related information or data	

Key Safety Findings	Relevance to human usage
Local tolerance: *PV0350101* *Investigation on Local Tolerance of Immune Globulin Intravenous (Human) 10% Triple Virally Reduced Solution in Rabbits* There were no macroscopic findings at injection sites of animals receiving IV infusions, whereas those of animals in the intra-arterial and paravenous treatment groups showed slight irritation. The observed reactions are considered to be a consequence of the animals' immune response to the human IgG preparation.	KIOVIG (IGIV, 10%) is considered well tolerated after IV application. 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 considered of limited relevance for human usage.
In vitro Hypersensitivity and General Pharmacology: *CHI-SR-DZ-004* *Assessment of TAK-880 for its potential to induce immune cell activation and cytokine/chemokine release in a human in vitro assay.* The results obtained for KIOVIG and TAK-880 from all eight blood donors and under both non-stimulatory and stimulatory conditions indicate a dose dependent stimulation of the immune system, as expected based on the IgG mechanisms of action. There was no difference between TAK-880 and KIOVIG in their ability to induce immune cell activation or the secretion of cytokines/chemokines, confirming that the effects of TAK-880 on cells of the human immune system are comparable to that of the known effects of KIOVIG. *CHI-SR-DZ-003* *Assessment of TAK-880 for its potential to activate complement in a human in vitro assay.* Incubation of whole blood with both KIOVIG and TAK-880 resulted in complement activation, which is an expected effect of IgGs. Activation didn't show a significant difference between TAK-880 and KIOVIG. In conclusion, the results obtained from all donors indicate that there was no increased potential of TAK-880 compared to KIOVIG in its ability to activate the complement system. *CHI-SR-DZ-005* *Assessment of TAK-880 for its potential to activate basophils in a human in vitro assay.* Incubation of whole blood with both KIOVIG and TAK-880 at all concentrations tested did not result in a significant increase of activated basophils compared to control. In conclusion, the results obtained under both non-stimulatory and stimulatory conditions indicate	The results of the safety pharmacology studies with KIOVIG (IGIV, 10%) demonstrated a safety profile that is comparable to that of the marketed immunoglobulin products. Therefore, the risk of an anaphylactoid or thrombogenic reaction after treatment with KIOVIG (IGIV, 10%) in patients is considered to be at least as rare as with other products. The TAK-880-specific studies demonstrated that there was no difference between TAK-880 and KIOVIG in their hypersensitivity potential. Importantly, the revealed differences in relative IgG4 concentrations between TAK-880 and KIOVIG did neither result in an increased anaphylactoid potential in vivo nor in differences in immune system stimulation in vitro under non-stimulatory and under stimulatory conditions. The data demonstrated that there is no increased safety risk associated with the effects of TAK-880 compared to KIOVIG.

Key Safety Findings	Relevance to human usage
that there was no increased potential of TAK-880 compared to KIOVIG to activate basophils. *PV0280101* *Anaphylactoid Potential of IGIV, 10 % triple virally reduced (TVR) Hypotensive Effect in SH-rats* Two (out of 18) anaphylactoid reactions. No increased risk for anaphylactoid reactions was seen for KIOVIG compared to GAMMAGARD S/D. *PV0310101* *Anaphylactoid Potential of IGIV,* *10 % TVR: Bronchospastic Activity in Guinea Pigs* No anaphylactoid reactions were observed. No increased risk for anaphylactoid reactions was seen for KIOVIG compared to GAMMAGARD S/D. *TKD-BCS-01044* *Anaphylactoid bronchospastic potential of TAK-880 in anaesthetized guinea pigs* IV administration of KIOVIG and TAK-880 showed no bronchospastic anaphylactoid potential in anaesthetized guinea pigs, with none of the animals exhibiting anaphylactoid potential in terms of bronchoconstriction. In conclusion, TAK-880 revealed no anaphylactoid potential in guinea pigs after IV administration. *TKD-BCS-01045* *Evaluation of Hypotensive Effect of TAK-880 in Spontaneously Hypertensive Rats* IV administration of KIOVIG and 2 lots of TAK-880 showed no anaphylactoid potential in terms of hypotension in spontaneous hypertensive rats. IV administration of the third lot of TAK-880 showed no anaphylactoid potential in terms of hypotensive in 5 out of 6 rats. As hypotension occurred in only 1 of 6 animals, the criteria for a positive response to the test item was not met. One reaction out of 6 animals is considered to be within the variability of the test system. In conclusion, TAK-880 revealed no increased anaphylactoid potential in rats after IV administration. *PV0320101* *Investigation of the Thrombogenic Potential of IGIV, 10 % TVR in a Rabbit Stasis Model* Minor thrombus formation was observed. The data indicate that KIOVIG has a lower thrombogenic potential than GAMMAGARD S/D.	

Part II: Module SIII - Clinical trial exposure

No clinical trials have been performed in specific to TAK-880. TAK-880 and KIOVIG essentially are comparable. The clinical trial data of KIOVIG can be extrapolated to TAK-880 and the data is presented below:

There have been 646 subjects exposed to KIOVIG across 10 clinical studies in 5 indications.

Study	Indication	Number of Subjects[a]
160001	Primary immunodeficiency disorders (PID)	22
160002	Idiopathic thrombocytopenic purpura (ITP)	23
160101	Primary immunodeficiency disorders (PID)	61
160601	Primary immunodeficiency disorders (PID) & Acute serious bacterial infections	49
160604	Multifocal Motor Neuropathy	44
160701	Alzheimer's Disease	262
161003	Alzheimer's Disease	168
BLB-010-001	Alzheimer's Disease	12
BLB-010-002	Alzheimer's Disease	5
161202	Alzheimer's Disease	4
Total		**646**
Randomized Studies (160101, 160604, 160701, 161003, BLB-010-001, BLB-010-002)		552
Non-randomized Studies (160001, 160002, 160601, 161202)		98
Cross-over Studies (160604)		44
Total		**646[a]**

[a]Unique subjects exposed to medicinal product in multiple trials are counted once in pooled summaries (One 160601 Subject participated in studies 160101 and 160601. Three 160701 Subjects participated in studies 160701 and 161202).

Table SIII.1: Duration of exposure

Cumulative for all indications (persons):	
Duration of exposure	**Persons**
0 to <0.5 years	180
0.5 to <1 year	197
1 to <2 years	268
2 to <3 years	1
3 or more years	0
Total person time	**646**

Indication: Primary Immunodeficiency (PID)	
Duration of exposure	**Persons**
0 to <0.5 years	7
0.5 to <1 year	62
1 to <2 years	39
2 to <3 years	1
3 or more years	0
Total person time	**109**

Indication: Multifocal Motor Neuropathy (MMN)	
Duration of exposure	**Persons**
0 to <0.5 years	1
0.5 to <1 year	42
1 to <2 years	1
2 to <3 years	0
3 or more years	0
Total person time	**44**

Indication: Idiopathic Thrombocytopenic Purpura (ITP)	
Duration of exposure	**Persons**
0 to <0.5 years	23
0.5 to <1 year	0
1 to <2 years	0
2 to <3 years	0
3 or more years	0
Total person time	**23**

Indication: Indication: Alzheimer's disease (AD)	
Duration of exposure	**Persons**
0 to <0.5 years	148
0.5 to <1 year	72
1 to <2 years	228
2 to <3 years	0
3 or more years	0
Total person time	**448**

Indication: Hypo- or Agammaglobulinemia	
Duration of exposure	**Persons**
0 to <0.5 years	1
0.5 to <1 year	21
1 to <2 years	0
2 to <3 years	0
3 or more years	0
Total person time	**22**

Table SIII.2: Age group and gender

	Persons		
Age group	**Male**	**Female**	**Total**
<18 years	22	17	39
18 to <65 years	147	115	262
65 to <75 years	79	96	175
75 or more years	78	92	170
Total Persons			**646**

Indication: Primary Immunodeficiency (PID)			
	Persons		
Age group	Male	Female	Total
<18 years	22	17	39
18 to <65 years	30	32	62
65 to <75 years	2	5	7
75 or more years	0	1	1
Total Persons			**109**

Indication: Multifocal Motor Neuropathy (MMN)			
Age group	Persons		
	Male	Female	Total
<18 years	0	0	0
18 to <65 years	28	11	39
65 to <75 years	4	1	5
75 or more years	0	0	0
Total Persons			**44**

Indication: Idiopathic Thrombocytopenic Purpura (ITP)			
Age group	Male	Female	Total
<18 years	0	0	0
18 to <65 years	13	9	22
65 to <75 years	0	1	1
75 or more years	0	0	0
Total Persons			**23**

Indication: Alzheimer's disease (AD)			
Age group	Persons		
	Male	Female	Total
<18 years	0	0	0
18 to <65 years	62	57	119
65 to <75 years	73	87	160
75 or more years	78	91	169
Total Persons			**448**

Indication: Hypo- or Agammaglobulinemia			
Age group	Persons		
	Male	Female	Total
<18 years	0	0	0
18 to <65 years	14	6	20
65 to <75 years	0	2	2
75 or more years	0	0	0
Total Persons			**22**

Table SIII.3: Dose

Cumulative Study Exposure (by Dose - Totals)

Total Subjects	
Dose Level	**Persons**
<0.5 g/kg/month	190
0.5 to <1.0 g/kg/month	389
1.0 to <2.0 g/kg/month	38
≥2.0 g/kg/month	29
Total	**646**

[redacted]

Clinical Study Exposure (by Dose by Indication)

Indication: Primary Immunodeficiency (PID)	
Dose Level	**Persons**
<0.5 g/kg/month	24
0.5 to <1.0 g/kg/month	75
1.0 to <2.0 g/kg/month	10
≥2.0 g/kg/month	0
Total person time	**109**

Indication: Multifocal Motor Neuropathy (MMN)	
Dose Level	**Persons**
<0.5 g/kg/month	1
0.5 to <1.0 g/kg/month	13
1.0 to <2.0 g/kg/month	25
≥2.0 g/kg/month	5
Total person time	**44**

Indication: Idiopathic Thrombocytopenic Purpura (ITP)	
Dose Level	**Persons**
<0.5 g/kg/month	0
0.5 to <1.0 g/kg/month	0
1.0 to <2.0 g/kg/month	0
≥2.0 g/kg/month	23
Total person time	**23**

Indication: Alzheimer's disease (AD)	
Dose Level	**Persons**
<0.5 g/kg/month	160
0.5 to <1.0 g/kg/month	284
1.0 to <2.0 g/kg/month	3
≥2.0 g/kg/month	1
Total person time	**448**

[redacted]

Indication: Hypo- or Agammaglobulinemia	
Dose Level	**Persons**
<0.5 g/kg/month	5
0.5 to <1.0 g/kg/month	17
1.0 to <2.0 g/kg/month	0
≥2.0 g/kg/month	0
Total person time	**22**

Clinical Study Exposure by Number of Infusions - Totals

Subjects Receiving 1 to 5 infusions	102
Subjects Receiving 6 to 10 infusions	73
Subjects Receiving 11 to 15 infusions	126
Subjects Receiving 16 to 20 infusions	49
Subjects Receiving 21 to 25 infusions	26
Subjects Receiving 26 to 30 infusions	16
Subjects Receiving more than 30 infusions	254
Total Subjects	**646**
Total Injections	**14 354**

SIII.4 Ethnic Origin

Clinical Study Exposure by Ethnic Origin (All Indications)

Ethnic origin	**Persons**
Asian	20
Black	16
Caucasian	590
Hispanic	18
Other	2
Total	**646**

Exposure by Ethnic Origin (by Indication)

Indication: Primary Immunodeficiency (PID)	
Ethnic origin	**Persons**
Asian	1
Black	5
Caucasian	102
Hispanic	1
Other	0
Unknown	0

[redacted]

Indication: Primary Immunodeficiency (PID)	
Ethnic origin	**Persons**
Total	**109**

Indication: Multifocal Motor Neuropathy (MMN)	
Ethnic origin	**Persons**
Asian	0
Black	2
Caucasian	41
Hispanic	1
Other	0
Unknown	0
Total	**44**

Indication: Idiopathic Thrombocytopenic Purpura (ITP)	
Ethnic origin	**Persons**
Asian	0
Black	0
Caucasian	23
Hispanic	0
Other	0
Unknown	0
Total	**23**

Indication: Alzheimer's disease (AD)	
Ethnic origin	**Persons**
Asian	19
Black	9
Caucasian	402
Hispanic	16
Other	2
Unknown	0
Total	**448**

[redacted]

Indication: Hypo- or Agammaglobulinemia	
Ethnic origin	**Persons**
Asian	0
Black	0
Caucasian	22
Hispanic	0
Other	0
Unknown	0
Total	**22**

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

No clinical trials have been performed with TAK-880. TAK-880 and KIOVIG essentially are comparable. The clinical trial data of KIOVIG can be extrapolated to TAK-880.

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

Subjects with a history of known allergy, hypersensitivity, or persistent reactions	
Reason for exclusion:	TAK-880 should not be used in patients with known hypersensitivity to human immunoglobulins.
Is it considered to be included as missing information?:	No
Rationale:	As with any product, hypersensitivity reactions are possible. Hypersensitivity is an important identified risk with the product. Hypersensitivity also remains a contraindication for use. Patients with hypersensitivity to the active substance or to the excipients should avoid using the product.

Subjects with IgA deficiency and known anti-IgA antibodies	
Reason for exclusion:	Administering an IgA containing product in patients with selective IgA deficiency with antibodies against IgA can result in anaphylaxis.
Is it considered to be included as missing information?:	No
Rationale:	Hypersensitivity including hypersensitivity against IgA is an important identified risk with the product.

Subjects with a history of thrombophilia or thrombotic episodes (e.g., deep vein thrombosis (DVT), myocardial infarction, cerebrovascular accident (CVA), pulmonary edema, or sickle cell anemia with history of painful vaso-occlusive crisis)	
Reason for exclusion:	TEEs are a known risk of intravenous immunoglobulin treatment. The risk of thrombosis by a new product cannot be justified until the efficacy of the product has been demonstrated.
Is it considered to be included as missing information?:	No
Rationale:	TEEs is an important identified risk with the use of the product.

Subjects with bleeding disorders or who were receiving anticoagulation therapy at the time of study enrolment	
Reason for exclusion:	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 subcutaneous infusions is increased in patients who are anti-coagulated.
Is it considered to be included as missing information?:	No
Rationale:	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 abnormal protein loss (e.g., protein losing enteropathy, nephrotic syndrome, or severe lung disease)	
Reason for exclusion:	It is impossible to do proper PK assessments in subjects with abnormal protein loss, so these subjects are excluded from clinical studies. Subjects who only have abnormal losses and not PID syndrome 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 normalization of insufficient immunoglobulin levels caused by these conditions.
Is it considered to be included as missing information?:	No
Rationale:	Physicians must perform a baseline assessment of all underlying diseases and weigh the benefit-risk balance for each individual prior to prescribing therapy. PID patients who also have abnormal protein loss are properly treated with replacement therapy while simultaneously addressing the cause of the abnormal losses.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions.

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	Not included in the clinical development program. The safety of KIOVIG in pregnancy and lactation has not been assessed in clinical trials. IVIg products have been shown to cross the placenta, increasingly during the third trimester.
Breastfeeding women	
Patients with relevant comorbidities: • 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 KIOVIG did not exclude subjects based on race or ethnic origin. The target indications for TAK-880 are known to occur in various ethnic and racial groups. It is unlikely that the safety of TAK-880 is affected by race or ethnicity. There are no contraindications for use of KIOVIG in patients of any racial or ethnic origin. However, limited information is available for the use of TAK-880 in patients of different ethnic origins as the majority of the subjects who participated in clinical trials were Caucasian.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program
Children	KIOVIG was evaluated in subjects between the ages 2 to 16, but there were a limited number of study subjects. KIOVIG administered intravenously was evaluated in 15 pediatric subjects with PID (7 between the age range of 2 to <12 years old and 8 between the age range of 12 to 16) in a multi-center clinical study. KIOVIG administered subcutaneously was evaluated in 18 pediatric subjects with PID (14 were 2 to <12 years old and 4 were 12 to <16) in another multi-center clinical study. There were no differences in the safety and efficacy profiles as compared with adult subjects. No pediatric-specific dose requirements were necessary to achieve the desired serum IgG levels. The safety and efficacy of KIOVIG/TAK-880 in pediatric patients below the age of 2 have not been established.

Part II: Module SV - Post-authorisation experience

Not applicable.

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 TAK-880 for illegal purposes.

Part II: Module SVII – Identified and potential risks

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

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

Potential risk: Off-label use

Off-label use can consist of use for unapproved indication, route of administration, dosage, population or use in contraindicated patients. The risk of off-label use is a potential risk with minimal clinical impact on patients (in relation to the severity of the indication treated). Although there are measures to prevent off-label use, such as TAK-880 being a prescription-only medicine, it is almost impossible to completely avoid off-label use in most medicines.

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

Important identified risk	Risk-benefit impact
Hypersensitivity	Hypersensitivity reactions to IGIV are rare, but can occur, especially in people with selective IgA deficiency (TAK-880 contains low IgA). The impact of such reactions may range from negligible to significant, depending on the acuity and severity of the reaction. Reactions can range from a mild rash to fatal anaphylactic reactions.
Haemolysis	In the case of a severe hemolytic event, patients may experience disability or life-threating/fatal outcomes requiring inpatient hospital care or long-term treatment. The outcome and seriousness vary widely and depend greatly on the timing of the diagnosis, initiation of treatment, and discontinuation of IG therapy.
TEEs	In the case of severe TEEs, patients may experience disability or life-threating/fatal outcomes requiring in-patient hospital care or long-term treatment.

Important potential risk	Risk-benefit impact
Transmittable infectious agents	The risk of viral contamination is a potential complication to all biological products whose production involves the use of human or animal material. Depending on the nature of the infectious agent and the severity of the event, patients may require inpatient hospital care.

Missing information	Risk-benefit impact
Lack of information in pregnant and lactating women	No clinical studies have been done in women who are pregnant or breast-feeding, so it is unknown whether it is safe for these women to take TAK-880.

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: Hypersensitivity	
Potential mechanisms:	Immune response to intravenous human immune globulin
Evidence source(s) and strength of evidence:	Medical literature, potential mechanism of action
Characterisation of the risk:	Hypersensitivity reactions have been reported in general, for intravenously administered immunoglobulin products. 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. Mild hypersensitivity reactions such as rash may not require treatment. However, severe reactions such as anaphylaxis may require significant medical intervention and very rarely lead to death. Hypersensitivity drug reactions represent approximately 10% to 20% of adverse drug reactions, which can affect 3% to 26% of the general population; depending on the age group [redacted]. Hypersensitivity reactions after treatment with IVIg are associated with symptoms that can include local inflammation as well as systemic reactions. Severe anaphylactic reactions can occur in any patient receiving IVIg; 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 [redacted] reported that 19 out of 23 (83%) IgA deficiency (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 [redacted].
Risk factors and risk groups:	Patients receiving IVIg treatment. Patients with selective IgA deficiency who developed antibodies to IgA, as administering an IgA containing product can result in anaphylaxis. TAK-880 is contraindicated in patients with known anaphylaxis or severe hypersensitivity to TAK-880 with less than 2 mcg/mL IgA in 10% solution.
Preventability:	If a patient's history of anaphylactic or severe hypersensitivity to human immune globulin is known, it should be noted in the medical records. Patients should be informed of the early signs of anaphylaxis/hypersensitivity (e.g., hives, pruritus, generalized 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:	The individual impact of such reactions may range from negligible to significant depending on the acuity and severity of the reaction.
Public health impact:	None

Important Identified Risk: Haemolysis	
Potential mechanisms	Immunoglobulin products can contain blood group antibodies that may act as haemolysins 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	Medical literature, post-Marketing reports
Characterisation of the risk	There were no known cases reported in clinical trials. Although the frequency with TAK-880 is unknown, hemolysis has been reported in association with other intravenously administered immunoglobulin products. The outcome and seriousness vary widely and depend greatly on the timing of the diagnosis, initiation of treatment, and discontinuation of IG therapy. A study was conducted to evaluate the relationship between IVIg use and development of hemolytic anemia, and prospective surveillance found that approximately 2.6% of the patients evaluated developed hemolytic anemia [redacted]. In a more recent study, 1.6% of patients (16 per 1,000) receiving IVIg were identified as hemolysis cases [redacted]. Hemolytic anemia represents approximately 5% of all anemias.
Risk factors and risk groups	Patients with blood groups A, B or AB, receiving immunoglobulin therapy are potentially at risk.
Preventability	Patients who are administered immunoglobulin products should be monitored for signs and symptoms of hemolysis. Patients should strictly adhere to the recommended rate of administration in the SmPC and PIL.
Impact on the risk-benefit balance of the product	In the case of a severe hemolytic event, patients may experience disability or life-threating/fatal outcomes requiring inpatient hospital care or long-term treatment.
Public health impact	Depending on the severity of the event, patients may need inpatient care and/or blood transfusion.

Important Identified Risk: Thromboembolic events (TEEs)	
Potential mechanisms	Increased blood viscosity is thought to be an important factor in the development of thromboembolic complications [redacted].
Evidence source(s) and strength of evidence	SmPC, Medical literature, post-marketing reports
Characterisation of the risk	There were no reported cases in clinical studies. However, thromboembolic events(TEEs) have been observed with KIOVIG administered intravenously. The outcome and seriousness of TEEs can vary widely. Deep venous thrombosis may resolve spontaneously with little sequelae, while stroke and myocardial infarction may result in significant disability or death. Thrombotic events continue to be a concern with all immunoglobulin products, but the reported rate remains low and stable over the years since KIOVIG was first approved. In addition, the majority of the TEEs presented with one or more additional risk-factors for the development of a thromboembolic episode (e.g., age, co-morbidities, etc.). The literature indicates that the presence of any single cardiovascular condition does not confer a significant risk of stroke or myocardial

Important Identified Risk: Thromboembolic events (TEEs)	
	infarction during IVIg 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 IVIg treatment were reported to be ten-fold higher when four or more cardiovascular risk factors are present[redacted] Previous reports examining TEEs associated with IVIg treatment have proposed risk factors including age, cardiovascular risk factors, and first-time exposure of IVIg [redacted]. The frequency of specific TEEs in the general European population are described below: Myocardial infarction: coronary artery disease is the most common cause of death in the Western world, and most of these deaths are due to myocardial infarction. Each year approximately 1.5 million patients experience a myocardial infarction; 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].
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 immobilization • Obesity • Diabetes mellitus, • Acquired or inherited thrombophilic disorder, • A history of vascular disease • A history of a previous thrombotic or thromboembolic event
Preventability	In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable. If a patient has known risk factors or is part of a risk group for TEEs, it should be noted in the patient records.
Impact on the risk-benefit balance of the product	In the case of severe TEEs, patients may experience disability or life-threating/fatal outcomes requiring inpatient hospital care or long-term treatment.
Public health impact	There is limited impact to public health. Depending on the severity of the event, patients may require in-patient hospital care.

Important Potential Risk: Transmittable infectious agents	
Potential mechanisms	Viral contamination of medicinal source material of human biologic origin. TAK-880 is made from human plasma. Several standard measures are taken to prevent infections resulting from the use of medicinal products prepared from human blood or plasma. Despite this, when medicinal

Important Potential Risk: Transmittable infectious agents	
	products prepared from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.
Evidence source(s) and strength of evidence	Medical literature
Characterisation of the risk	The protective measures taken for TAK-880 are considered effective for enveloped viruses such as HIV, hepatitis B virus (HBV), hepatitis C virus (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. The risk of viral contamination 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, e.g., viruses and, theoretically, Creutzfeldt-Jakob disease (CJD), hepatitis virus, and HIV. The frequency of potential infectious agents in the general population is described below: Creutzfeldt-Jakob disease (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[redacted]. HBV infection varies worldwide, with chronic HBV prevalence ranging from 0.2% to 20%[redacted]. In the European region, approximately 14 million people are chronically infected with HBV [redacted]. Overall, the transmission risk of infectious agents from donated blood products has decreased by three to four orders of magnitude over the past thirty years[redacted].
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, and HCV, and for the nonenveloped viruses HAV and parvovirus B19.
Impact on the risk-benefit balance of the product	Depending on the nature of the infectious agent and the severity of the event, patients may require inpatient hospital care.
Public health impact	Depending on the nature and transmission pathway of the infectious agent, the potential for widespread transmission cannot be excluded.

[redacted]

SVII.3.2. Presentation of the missing information

Missing Information: Lack of Information in Pregnant and Lactating Women	
Evidence source:	No clinical studies have been done in women who are pregnant or breast-feeding. **Population in need of further characterisation:** Pregnant and/or breast-feeding women

[redacted]

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important Identified Risks	Hypersensitivity
	Haemolysis
	Thromboembolic events (TEEs)
Important Potential Risks	Transmittable infectious agents
Missing Information	Lack of information in pregnant and lactating women

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

III.1. Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for Hypersensitivity:

Standardized collection of information via hypersensitivity (allergy) questionnaire to facilitate better characterisation of the risk.

Specific adverse reaction follow-up questionnaires for TEEs:

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

Other forms of routine pharmacovigilance activities:

None

III.2. Additional pharmacovigilance activities

There are no additional pharmacovigilance activities proposed for TAK-880.

III.3. Summary Table of additional Pharmacovigilance activities

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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None.				
Category 3 - Required additional pharmacovigilance activities				
None.				

Part IV: Plans for post-authorisation efficacy studies

Several studies were conducted with KIOVIG/GAMMAGARD LIQUID in patients with primary and secondary immunodeficiency syndromes as well as in patients with ITP, GBS, MMN and Kawasaki disease.

Based on the clinical evidence arising from these studies demonstrating the efficacy and tolerability for intravenous KIOVIG, there is no need for further post-authorisation efficacy studies for TAK-880.

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 Risk: Hypersensitivity	**Routine risk communication:** SmPC Section 4.3, Contraindications SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects. PL Section 2, What you need to know before you use Deqsiga and Section 4, Possible side effects **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 Identified Risk: Haemolysis	**Routine risk communication:** SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects PL Section 4, Possible side effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 Special warnings and precautions for use IVIg products can contain blood group antibodies which may act as haemolysins and induce in vivo coating of red blood cells with immunoglobulin, causing a positive direct antiglobulin reaction (Coombs' test) and, rarely, haemolysis. Haemolytic anaemia can develop subsequent to immunoglobulin therapy due to enhanced red blood cells (RBC) sequestration. Immunoglobulin product recipients should be monitored for clinical signs and symptoms of haemolysis. **Other routine risk minimisation measures beyond the Product Information:** None proposed
Important Identified Risk: TEEs	**Routine risk communication:** SmPC Section 4.4, Special warnings and precautions for use SmPC Section 4.8, Undesirable effects PL Section 2, What you need to know before you use Deqsiga **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4, Special warnings and precautions for use (Thromboembolism): In patients at risk for thromboembolic adverse reactions, IVIg products should be administered at the minimum rate of infusion and dose practicable.

Safety concern	Routine risk minimisation activities
	Other routine risk minimisation measures beyond the Product Information: None proposed
Important Potential Risk: Transmittable infectious agents	**Routine risk communication:** SmPC Section 4.4, Special warnings and precautions for use **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4, Special warnings and precautions for use (Transmissible agents): It is strongly recommended that every time that TAK-880 is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product. **Other routine risk minimisation measures beyond the Product Information:** None proposed
Missing Information: Lack of information in pregnant and lactating women	**Routine risk communication:** SmPC Section 4.6, Fertility, pregnancy and lactation PL Section 2 What you need to know before you use Deqsiga **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** None proposed

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

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 activities	Pharmacovigilance activities
Hypersensitivity	**Routine risk minimisation measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Hypersensitivity (Allergy) questionnaire **Additional pharmacovigilance activities:** None
Haemolysis	**Routine risk minimisation measures:** SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
TEEs	**Routine risk minimisation measures:** SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** TEE questionnaire **Additional pharmacovigilance activities:** None
Transmittable infectious agents	**Routine risk minimisation measures:** SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Lack of information in pregnant and lactating women	**Routine risk minimisation measures:** None **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Part VI: Summary of the risk management plan

Summary of risk management plan for TAK-880 (Human Normal Immunoglobulin [IVIg])

This is a summary of the risk management plan (RMP) for TAK-880. The RMP details important risks of TAK-880, how these risks can be minimised, and how more information will be obtained about TAK-880's risks and uncertainties (missing information).

TAK-880's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how TAK-880 should be used.

This summary of the RMP for TAK-880 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 TAK-880's RMP.

I. The medicine and what it is used for

TAK-880 is authorised for the replacement therapy in primary immunodeficiency syndromes in adults, and children and adolescents (0-18 years) in: PID with impaired antibody production, as well as SID in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either PSAF or serum IgG level of <4 g/l, where PSAF = failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccines.

In addition, TAK-880 is approved for immunomodulation in adults, children and adolescents (0-18 years) in: Primary ITP, in patients at high risk of bleeding or prior to surgery to correct the platelet count; Guillain Barré syndrome; Kawasaki disease (in conjunction with acetylsalicylic acid); CIDP and MMN (see SmPC for the full indication). It contains Human Normal Immunoglobulin (IVIg) as the active substance, and it is administered via the intravenous route.

Further information about the evaluation of TAK-880's benefits can be found in TAK-880's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

LINK TO THE EPAR SUMMARY LANDING PAGE.

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

Important risks of TAK-880, together with measures to minimise such risks and the proposed studies for learning more about TAK-880'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 package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The 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, 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 TAK-880 is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of TAK-880 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 TAK-880. 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	Hypersensitivity
	Haemolysis
	Thromboembolic events (TEEs)
Important potential risks	Transmittable infectious agents
Missing information	Lack of information in pregnant and lactating women

II.B Summary of important risks

Important Identified Risk: Hypersensitivity	
Evidence for linking the risk to the medicine	Medical literature, potential mechanism of action
Risk factors and risk groups	Patients receiving IVIg treatment. Patients with antibodies to IgA or low IgA levels may be at higher risk and should receive the product when treatment with IVIg is clearly indicated. These patients should receive the product under close supervision where supportive care is available. IVIg is contraindicated in patients with selective IgA deficiency when the patient has antibodies against IgA because administration of IgA-containing product in such patients can result in anaphylaxis.
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Important Identified Risk: Haemolysis	
Evidence for linking the risk to the medicine	Medical literature, post-Marketing reports
Risk factors and risk groups	Patients with blood groups A, B or AB, receiving immunoglobulin therapy are potentially at risk
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

[redacted]

Important Identified Risk: : Thromboembolic Events(TEEs)	
Evidence for linking the risk to the medicine	SmPC, 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 immobilization • Obesity • Diabetes mellitus, • Acquired or inherited thrombophilic disorder, • A history of vascular disease • A history of a previous thrombotic or thromboembolic event
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Important Potential RiskTransmittable 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
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Section 4.4 Special warnings and precautions for use **Additional risk minimization measures:** None
Additional pharmacovigilance activities	None

Missing Information: Lack of Information in Pregnant and Lactating Women	
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None

[redacted]

Missing Information: Lack of Information in Pregnant and Lactating Women	
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 TAK-880.

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

There are no studies required for TAK-880.

[redacted]

Part VII: Annexes

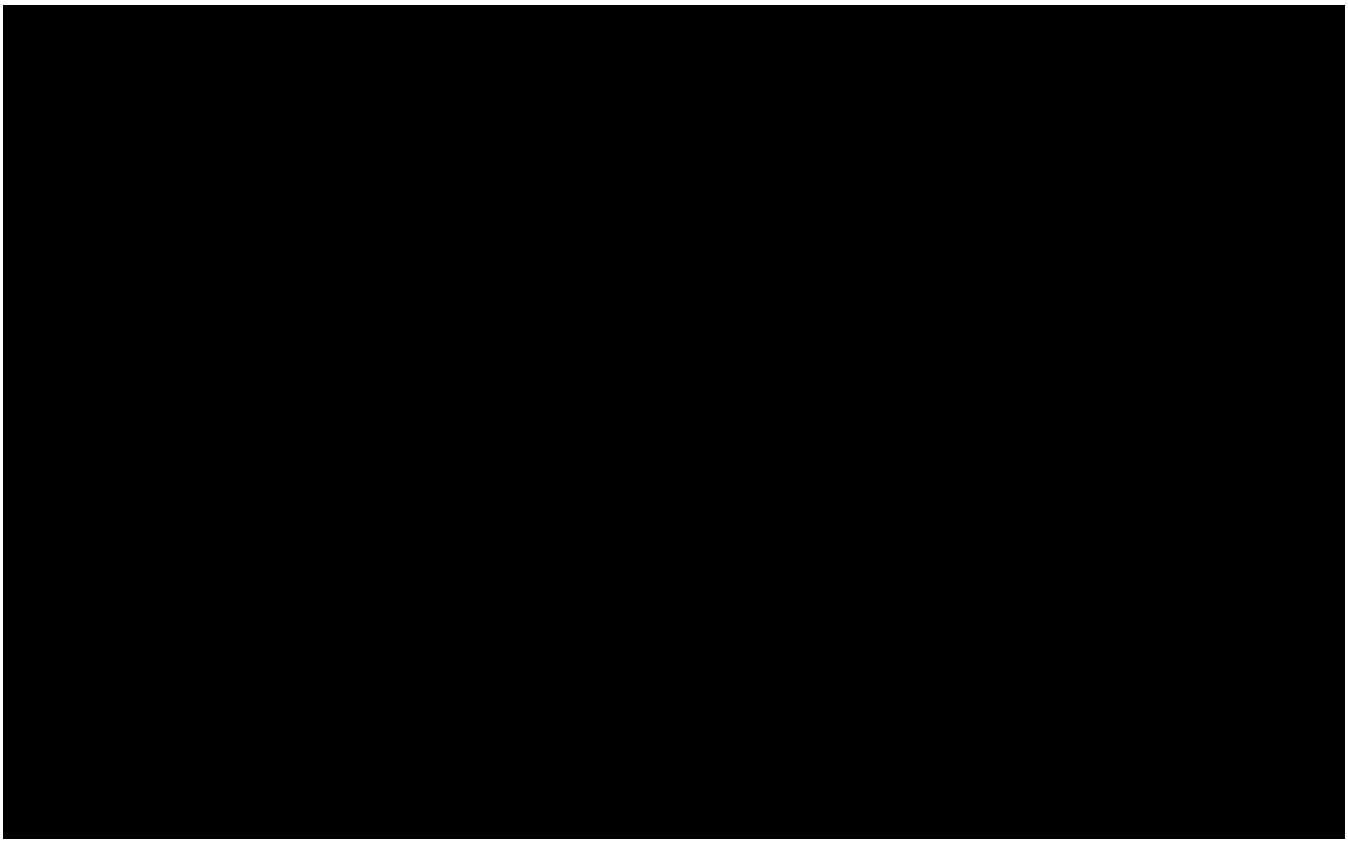
Table of contents

[redacted]

[redacted]

[redacted]

[redacted]



Annex 4: Specific adverse drug reaction follow-up forms

Annex 4.1: The Hypersensitivity (Allergy) Questionnaire

Annex 4.2: TEE Questionnaire

Annex 4.1: The Hypersensitivity (Allergy) Questionnaire

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

1. PATIENT INFORMATION

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

2. Drug: _____

Indication for Use (type of PID):

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

Date of first Dose (dd/mmm/yyyy):		Date of Latest Dose (dd/mmm/yyyy):	
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

☐ Was drug treatment continued after Adverse Event remission

☐ Was drug treatment 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)

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

Systemic Reactions

☐ Urticaria	☐ Generalized Itching (esp. groin or axillae)
☐ Tightness in Throat	☐ Hoarseness
☐ 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 (dd/mmm/yyyy):

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

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

Diagnosis	State Date (dd/mmm/yyyy)	Stop Date (dd/mmm/yyyy)	Check if ongoing
			☐
			☐
			☐
			☐
			☐
			☐
			☐
			☐

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

Annex 4.2: 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/TAK-339/TAK880 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)*

General (e.g., bedridden or prolonged bed rest > 3 days)	☐
Limb immobilization (e.g., cast)	☐

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

CONCOMITANT MEDICATIONS

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

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

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

Not applicable