EU RISK MANAGEMENT PLAN (RMP)

Jivi

BAY94-9027
(Damoctocog Alfa Pegol)

No. 3.3

Date of Report:
02 APR 2025

[redacted]

EU Risk Management Plan for Jivi (Damoctocog Alfa Pegol)

RMP version to be assessed as part of this application:

RMP Version number: 3.3

Data lock point for this RMP: 31 MAR 2024

Date of final sign-off: 02 APR 2025

Rationale for submitting an updated RMP:

- Proposed extension of the indication to include previously treated patients (PTP) ≥7 years of age (Procedure: EMEA/H/C/004054/II/0034)
- Updates following committee for medicinal products for human use (CHMP) Co-Rapporteur and pharmacovigilance risk assessment committee (PRAC) Rapporteur's assessment report in Procedure EMEA/H/C/004054/II/0034
- Addition of new dose strength (4,000 IU) (Procedure EMEA/H/C/004054/X/0033/G (4,000 IU Dose)
- Addition of data from a completed part A of a paediatric study (Study number [SN] 21824, Alfa-PROTECT), which has been integrated into the safety pool to support extension of the indication to include previously treated children aged 7 years and above with haemophilia A (Final Study Report B002892, from 18 JUN 2024 [finalised after the data lock point {DLP} of this report]).
- Removal of the Category 3 Post-Authorization Safey Study (PASS): Post-marketing investigation (PMI) study to assess safety and efficacy of Jivi (SN 19764 from the list of additional pharmacovigilance activities due to study completion [Final study report: PH-42467, 15 MAY 2023]).

Summary of significant changes in this RMP (in comparison to version 2.1):

- PART I - Table I.1 updated to include the proposed extension of the indication to PTPs children aged ≥7 years with haemophilia A, and the respective dosing information. New dose strength (4,000 IU) was added.
- PART II: Module SI - Update on currently available treatment options.
- PART II: Module SII - No significant changes.
- PART II: Module SIII - Clinical trial exposure final pooled data has been updated to include Alfa-PROTECT study (part A) and PMI study.
- PART II: Module SIV - Minor update to add information from Alfa-PROTECT study (paediatric experience) and experience in patients >65 years of age in PMI study.
- PART II: Module SV - Post-authorization exposure data included as of 31 MAR 2024.
- PART II: Module SVI - No significant changes.
- PART II: Module SVII - All safety concerns were reviewed and updated with relevant information from the completed SN 19764 and SN 21824 (part A) and from the post-marketing experience.
- PART II: Module SVIII - No changes.

- Part III – As the post-marketing investigation (PMI) study (SN 19764) has been completed, it is removed from the respective section of additional pharmacovigilance activities.
- Part IV – No significant changes.
- Part V – Additional pharmacovigilance activities updated to remove the PMI study (SN 19764). Completion date of data collection from the EUHASS registry and clarification on the reporting format added. Annual submission of update reports from the EUHASS registry to the European Medicines Agency (EMA) is removed; submission of EUHASS reports as part of the Periodic Safety Update Report (PSUR) added.
- Part VI – Summary was updated to reflect the changes introduced to the respective modules of this EU RMP.
- Part VII: – Updated to align with the RMP updates.

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version number: 2.1

Approved with procedure: EMEA/H/C/004054/IB/0018

Date of approval: 22 JUL 2021

QPPV signature:

EU QPPV name	Dr. Jutta Pospisil
Contact person for this RMP	[redacted]
Email address of contact person	[redacted]

Electronic QPPV signature is attached at the end of the document.

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List of abbreviations

%	Percent
>	Greater than
≥	Greater than or equal to
<	Less than
≤	Less than or equal to
β	Beta
γ	Gamma
$	Dollar
AAV	Adeno-Associated Virus
ACS	Acute Coronary Syndrome
ADA	Anti-Drug Antibodies
AE	Adverse Event
AFSSAPS	*Agence Française de Sécurité Sanitaire Des Produits De Santé*, The French Medicines and Healthcare Products Regulatory Agency
AHA	Acquired Haemophilia A
AICE	*Associazione Italiana Centri Emofilia* (Italian Association of Haemophilia Centres)
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
APC	Antigen-Presenting Cell
aPCC	activated Prothrombin Complex Concentrate
AR	Adverse Reaction
ASHD	Atherosclerotic Heart disease
AST	Aspartate Aminotransferase

ATC	Anatomical Therapeutic Chemical
BDD	B-Domain Deleted
BHK	Baby Hamster Kidney
BMD	Bone Mineral Density
BMI	Body Mass Index
BU	Bethesda Units
$CaCl_2$	Calcium Chloride
CACS	Coronary Artery Calcifications Score
CANAL	Concerted Action on Neutralizing Antibodies in severe haemophilia A
CFC	Coagulation Factor Concentrates
CHAFEA	European Commission's Consumers, Health and Food Executive Agency
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CKD	Chronic Kidney Disease
COX-2	Cyclooxygenase-2
cRMP	Core Risk Management Plan
CVAD	Central Venous Access Device
CVD	Cardiovascular Disease
DCSI	Development Core Safety Information
DLP	Data Lock Point
DNA	Deoxyribonucleic Acid
ECH	Extra-Cranial Haemorrhage
ED	Exposure Day
EEA	European Economic Area

EHTSB	European Haemophilia Therapy Standardisation Board
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESLD	End-Stage Liver Disease
EU	European Union
EUHASS	EUropean HAemophilia Safety Surveillance
F8	Factor VIII Gene
FDA	Food and Drug Administration
FIX	Factor IX
FL	Full-Length
FPFV	First Patient First Visit
FVIII	Factor VIII
FVIII:C	FVIII Coagulant
GNP	Gross National Product
GVP	Good Pharmacovigilance Practices
HAART	Highly Active Anti-Retroviral Therapy
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
HR	Hazard Ratio
HTC	Haemophilia Treatment Centre
ICH	Intracranial Haemorrhage

ICD	International Code for Diseases
IFN	Interferon
IgG/M/E	Immunoglobulin G/M/E
IL	Interleukin
IMT	Intima-Media Thickness
INN	International Nonproprietary Names
IQR	Interquartile
ISTH	International Society on Thrombosis and Haemostasis
ITI	Immune Tolerance Induction
IU	International Unit
JOS	Joint Outcome Study
L	Litre
LDL	Low-Density Lipoprotein
LODE	Loss of Drug Effect
LoE	Loss of Efficacy
LLOQ	Lower Limit of Quantification
LLT	Lowest Level Term
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MHC	Major Histocompatibility Complex
mAB	Monoclonal Antibodies
mPEG	Monomethoxy PEG
MTP	Minimally Treated Patient

n	Number of Patients
N	Total Number of Patients in the Population
NA	Not Available
N/A	Not Applicable
NAB	Neutralizing Antibodies
NaCl	Sodium Chloride
ND	Not Done
Neg	Negative
NOAEL	No Observed Adverse Effect Level
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NR	Not Reported
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSAID	Non-Steroidal Anti-Inflammatory Drug
OECD	Organization for Economic Co-operation and Development
OR	Odds Ratio
PASS	Post-authorisation Safety Study
PBRER	Periodic Benefit-risk Evaluation Report
pdFVIII	Plasma-derived FVIII
PEG	Polyethylene Glycol
PI	Protease Inhibitor
PK	Pharmacokinetics
PMI	Post-Marketing Investigation
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report

PT	Preferred Term
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
PV	Pharmacovigilance
PWH	Patients with Haemophilia
PWHA	Patients with Haemophilia A
PWHB	Patients with Haemophilia B
QPPV	Qualified Person Responsible for Pharmacovigilance
rFVIII	Recombinant Factor VIII
rFVIIa	Recombinant Activated FVII
RMP	Risk Management Plan
RNAi	Ribonucleic Acid interference
RPs	Radiolucent Periapical Lesion
SAE	Serious Adverse Event
SERM	Selective Oestrogen Receptor Modulator
SIPPET	Survey of Inhibitors in Plasma-Products Exposed Toddlers
SMD	Standardised Mean Difference
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SMR	Standardised Mortality Ratio
TEAE	Treatment-Emergent Adverse Event
TFPI	Tissue Factor Pathway Inhibitor
UK	United Kingdom
UKHCDO	United Kingdom Haemophilia Centre Doctors' Organization

ULN	Upper Limit of Normal
US(A)	United States (of America)
vWF	Von Willebrand Factor
WFH	World Federation of Haemophilia
Y	Yes

PART I: Product(s) overview

Table Part I-1 – Product(s) overview

Active substance(s) (INN or common name):	Damoctocog alfa pegol
Pharmaco-therapeutic group (ATC Code):	B02BD02
Marketing Authorisation Holder	Bayer AG
Medicinal products to which this Risk Management Plan (RMP) refers:	1
Invented name(s) in the European Economic Area (EEA)	Jivi
Marketing authorisation procedure	Centralised
Brief description of the product	Jivi is an anti-haemorrhagic blood coagulation factor VIII (FVIII) that serves to replace the deficient levels of FVIII present in patients with Haemophilia A. Jivi is a sterile, stable, purified, non-pyrogenic, dried protein concentrate of recombinant blood clotting recombinant Factor VIII (rFVIII). It is a recombinant B-domain deleted (BDD) human coagulation FVIII variant that is site-specifically conjugated with a single 60 kDa branched polyethylene glycol (PEG) at an engineered cysteine replacing the amino acid in position 1,804. Jivi is produced using standard recombinant technology in baby hamster kidney cells (BHK21) into which the human FVIII gene has been introduced. BHK21 is the same host cell line used for the licensed full-length (FL)-rFVIII, Kogenate FS/Kogenate Bayer. Jivi is then purified with conventional chromatographic procedures. The purification process includes steps of viral clearance and clearance of host cell impurities before PEGylation. The purified FVIII undergoes a cysteine-specific PEGylation and subsequent purification with a cation exchange column. The formulation for Jivi contains a combination of standard excipients (NaCl, $CaCl_2$, histidine, glycine, sucrose and Tween-80) with the same concentration as for the marketed FL-rFVIII, Kogenate FS/Kogenate Bayer. Jivi, like FL-rFVIII (Kogenate FS/Kogenate Bayer or BAY 14-2222), is an inactive zymogen and after activation acts as a cofactor in the intrinsic coagulation pathway, but with an extended circulation half-life due to the PEG moiety.
Hyperlink to the Product Information	Approved Product Information is available in **Module 1.3.1**

Part I: Product(s) Overview

Table Part I-1 – Product(s) overview

Indication(s) in the EEA	Current: Jivi is indicated for the treatment and prophylaxis of bleeding in in previously treated patients (PTPs) aged ≥12 years of age with haemophilia A (congenital FVIII deficiency).
	Proposed: Treatment and prophylaxis of bleeding in previously treated patients (PTPs) ≥7 years of age with haemophilia A.
Dosage in the EEA	Current: For prophylaxis: • 45–60 IU/kg every 5 days; based on patient clinical phenotype the dose can also be 60 IU/kg every 7 days or 30–40 IU/kg 2 times per week. Minor surgery including tooth extraction: • FVIII Level Required (%) (IU/dL): 30–60 • Frequency of Doses (hours)/Duration of Therapy (days): Every 24 hours, at least 1 day, until healing is achieved. Major Surgery: • FVIII Level Required (%) (IU/dL): 80–100 (pre- and postoperative) • Frequency of Doses (hours)/Duration of Therapy (days): Repeat dose every 12–24 hours until adequate wound healing, then therapy for at least another 7 days to maintain FVIII activity of 30–60% (IU/dL).
	Proposed: (….) For prophylaxis: Adults and adolescents (12 years of age and older) 45–60 IU/kg every 5 days; based on patient clinical phenotype the prophylaxis regimen can also be 60 IU/kg every 7 days or 30-40 IU/kg two times per week. Children (7 to <12 years of age): For prophylaxis the regimen is: 40-60 IU/kg two times per week. The recommended starting dose is: 60 IU/kg two times per week.
Pharmaceutical form(s) and strengths	Current: Jivi is a sterile lyophilised powder for injection supplied with the appropriate amount of water for injection. Jivi is provided in vials containing 250 IU, 500 IU, 1,000 IU, 2,000 IU or 3,000 IU of FVIII activity potency to be reconstituted with 2.5 mL of water for injection.

Part I: Product(s) Overview

Table Part I-1 – Product(s) overview

	Proposed: Jivi is approved as sterile, stable, purified dried concentrate (lyophilized powder), and is reconstituted with sterile water for injection. It is approved in six vial sizes (250 international units [IU], 500 IU, 1,000 IU, 2,000 IU, 3,000 IU and 4,000 IU).
Is/will the product be subject to additional monitoring in the EU?	No

PART II: Safety Specification

PART II: Module SI - Epidemiology of the indication and target population

SI.1 Indication

Jivi is indicated for the treatment and prophylaxis of bleeding in previously treated patients (PTPs) aged ≥12 years of age with haemophilia A (congenital factor VIII [FVIII] deficiency). Proposed indication is for treatment and prophylaxis of bleeding in previously treated patients (PTPs) ≥7 years of age with haemophilia A.

Haemophilia A is a member of a group of diseases (also including haemophilia B) that have an X-linked recessive mode of inheritance, such that most affected individuals are men. Women are unlikely to express the disease but can be carriers. Most patients with haemophilia (PWH; 80%-85%) are classified as having haemophilia A and 15%-20% as having haemophilia B (deficient in factor IX [FIX]) (1, 2). Haemophilia A is caused by mutations in the blood coagulation FVIII gene (*F8*). There is a 50% chance that a carrier mother will transmit the defective X-linked gene to a child. All female offspring born to a haemophiliac father are obligatory carriers (3). Affected patients have a defect or a deficiency in FVIII. Depending on the levels of circulating FVIII coagulant (FVIII:C), haemophilia A is classified as follows:

- Severe <0.01 IU/mL (<1% of normal)
- Moderate 0.01–0.05 IU/mL (1%–5% of normal)
- Mild >0.05–<0.40 IU/mL (>5% – <40% of normal)

Where normal is 1.0 IU/mL or 100% FVIII: C (100%) (4)

Patients with severe haemophilia A are characterised by a high bleeding tendency with frequent spontaneous joint and muscle bleeds. In contrast, bleeds in patients with mild haemophilia occur only after trauma or surgery. Outcomes of patients with moderate haemophilia are in-between those with severe and mild disease, although a substantial burden of disease with bleeds and joint impairment is reported (5).

Acquired haemophilia A (AHA) is a rare but severe autoimmune bleeding disease occurring in non-haemophiliac patients (6). Acquired haemophilia A is not a target indication for damoctocog alfa pegol.

SI.1.1 Incidence and prevalence

Large variability in the reported prevalence and incidence of haemophilia A may exist owing to secular trends in the epidemiological data, inaccurate reporting practices of the disease, and premature death resulting from poor availability of FVIII treatment.

Incidence

Haemophilia A is a worldwide disease affecting all races and ethnic groups and all geographical areas. The World Federation of Haemophilia (WFH) guidelines, published in 2013, report the estimated frequency of haemophilia to be approximately 10 in 100,000 births

(2). A study in the United States of America (USA) reported a mean incidence over a 10-year period of 20 per 100,000 live male births, with annual incidences ranging from 18 to 22 per 100,000 live male births (7). In Sweden, the 3-year average incidence ranged from 36 per 100,000 people in 1998-2000 to 21 per 100,000 people in 2004-2006 (8).

The severe form of haemophilia A accounts for about 60% of the cases whereas moderate and mild forms account for about 20% each.

Prevalence

The prevalence of haemophilia (A and B), as reported by the WFH in 2002, varies widely among geographic regions, from 0.1-0.9 per 100,000 inhabitants in Southeast Asian countries to 0.2-19.9 per 100,000 inhabitants in European countries (9). This large variability can be explained by differences in the economic status of individual countries, which may affect reporting practices, availability and quality of treatment and life expectancy. The same considerations apply to data regarding haemophilia A alone, for which the prevalence per 100,000 inhabitants in the WFH 2015 Global Survey ranged from 0.07 in Ethiopia to 12.95 in Ireland (10). An analysis of the prevalence data collected by the WFH Annual Global Survey from 1998 to 2006 showed that the prevalence of haemophilia A (per 100,000 males) for high-income countries was 12.8 ± 6.0 (mean ± SD) whereas it was 6.6 ± 4.8 for the rest of the world. The overall prevalence for all countries was 8.4 ± 5.9 per 100,000 males and for low income countries was 1.7 ± 1.7 per 100,000 males (11). An analysis of the published literature found that, within a country, there was a strong trend of increasing prevalence over time. The prevalence (per 100,000 males) in Canada ranged from 10.2 in 1989 to 14.3 in 2008 and the prevalence (per 100,000 males) in the United Kingdom (UK) ranged from 9.3 in 1974 to 21.6 in 2006 (11).

Table SI-1 and Table SI-2 below show the prevalence of haemophilia A per 100,000 males for countries that participated in the WFH Annual Global Surveys and reported prevalence in literature for high-income Organization for Economic Co-operation and Development (OECD) countries (11).

Table SI-1: Reported prevalence of haemophilia A in the World Federation Haemophilia annual survey (per 100,000 males)

Country	1998–2006 Mean (SD)	2007[a] (2006–2007)	2008[b] (2003–2008)	2009[b] (2005–2009)	2010[c] (2005–2009)
Canada	13.2 (1.0)	14.8	15.4	15.6	NA
Finland	8.9 (0.3)	9.7	9.6	9.8	NA
France	12.2 (1.9)	11.3	12.4	13.2	NA
Germany	10.4 (1.3)	9.4	7.9	8.4	NA
Greece	12.2 (0.9)	12.5	13.0	12.7	12.7
Italy	11.7 (2.3)	9.0	9.1	9.0	9.1
Netherlands	17.2 (1.3)	14.5	14.3	13.9	13.7
Spain	8.8 (1.3)	7.1	6.8	6.9	NA
Sweden	15.3 (0.5)	25.5	17.9	17.6	17.7

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

Table SI-1: Reported prevalence of haemophilia A in the World Federation Haemophilia annual survey (per 100,000 males)

Country	1998–2006 Mean (SD)	2007[a] (2006–2007)	2008[b] (2003–2008)	2009[b] (2005–2009)	2010[c] (2005–2009)
United Kingdom	19.1 (2.0)	16.1	16.3	17.0	NA
United States	7.8 (0.1)	8.5	8.7	8.8	NA

Adapted from (11).
[a] Assuming gender breakdown for haemophilia A of 97.9 % for males.
[b] Assuming gender breakdown for haemophilia A of 97.7 % for males
[c] Assuming gender breakdown for haemophilia A of 97.7 % for males.
NA: OECD data used for calculation are not available.
NA: Not Available; SD: Standard Deviation

Table SI-2: Reported haemophilia A prevalence in the literature for high-income OECD countries (per 100,000 males)

Country	Year	Prevalence	
		Overall[a]	Severe
Canada	2008	14.3	4.3
Finland	1989	7.3	4.6
France	2001	15.0	NA
Germany	NA	NA	NA
Greece	1992	12.0	3.6
Italy	2006	9.5	4.8
Netherlands	2001	11.7	NA
Spain	1974	5.3	NA
Sweden	1980	11.0	3.3
United Kingdom	2008	21.5	7.1
United States	1998	10.4	4.4

Adapted from (11).
[a] Overall prevalence includes people with mild, moderate, and severe haemophilia A.
NA: Not Available; OECD: Organization for Economic Co-operation and Development.

These prevalence estimates may appear low considering the reported incidence of 10-20 per 100,000 male births. This can be explained by the fact that at the time of childbirth, data are, in general, captured routinely within a professional healthcare environment. This reduces the likelihood of under-reporting, which is possibly more prevalent in outpatient or other settings later in life. A low prevalence estimate may also reflect a low life expectancy for people with haemophilia from certain regions or treatment eras. In addition, people with mild or moderate haemophilia may have been included in incidence estimates but not in prevalence estimates.

In summary, haemophilia A affects all ethnic groups, although the prevalence varies widely between regions, with large variations between low- and high- income countries.

Within individual countries there is a strong trend of increasing prevalence of haemophilia A over time.

SI.1.2 Demographics of the target population

The 2015 WFH Global Survey reported gender data on 151,159 patients with haemophilia A (PWHA) from 108 participating countries: 91.1% were male, 2.6% were female, and 6.2% had unknown gender (10).

Age was reported for 68,500 patients (72 countries); overall the majority of the patients reported were adults (Table SI-3). Nevertheless, countries with the lowest level per capita gross national product (GNP) have haemophilia populations that are primarily 18 years of age and younger (Table SI-4). Given that the incidence of haemophilia, which is usually measured in infancy, is the same for all populations, the decrease in the numbers of adults in a population is assumed to reflect the effects of mortality (9).

Table SI-3: Overall age distribution of people with haemophilia A

Age, years	Reported patients N (%)			
	WFH global survey 2009	WFH global survey 2010	WFH global survey 2011	WFH global survey 2013[a]
0-4	3,494 (6)	4,200 (5)	5,917 (7)	5,403 (5)
5-13	10,352 (17)	12,789 (17)	15,083 (17)	12,303 (11)
14-18	6,892 (11)	8,290 (11)	9,660 (11)	8,654 (8)
19-44	26,401 (43)	33,405 (44)	35,461 (38)	30,163 (27)
45+	11,759 (19)	14,920 (20)	14,202 (16)	12,106 (11)
unknown	2,101 (3)	2,812 (4)	8,972 (10)	43,115 (39)
Total	60,999 (100)	76,416 (100)	90,295 (100)	111,743 (100)

Adapted from (12-15).
[a] WFH global survey 2013 only reported percentages, so N values are calculated.
N: Number; WFH: World Federation of Haemophilia: %: Percent.

Table SI-4: Age distribution in haemophilia A according to economic ranking

Age, years	High income economy (%)	Upper middle-income economy (%)	Lower middle-income economy (%)	Low-income economy (%)
0–4	5	5	8	8
5–13	14	17	22	32
14–18	10	12	14	24
19–44	42	45	44	35

Table SI-4: Age distribution in haemophilia A according to economic ranking

Age, years	High income economy (%)	Upper middle-income economy (%)	Lower middle-income economy (%)	Low-income economy (%)
45 +	29	16	9	5
unknown	1	6	3	-

Adapted from (12, 13).
Categories are based on the World Bank rankings for 2009 gross national income in US dollars ($): low income, $995 or less; lower middle income, $996–3,945; upper middle income, $3,946–12,195; and high income, >$12,196).
%: Percent

Haemophilia affects individuals of all races and ethnic backgrounds. A review of data from US haemophilia treatment centres (HTCs) reported that in 2010, 71% of patients at the centres were white, 13% Hispanic, 9% black and 7% "other" (16).

SI.1.3 Risk factors for the disease

Family history of haemophilia and a carrier mother are the main risk factors for haemophilia A.

Approximately two thirds of PWH have a family history of bleeding (17). In the remaining one third of patients, haemophilia results from spontaneous gene mutation. In such cases, 80% of mothers are carriers of a *de novo* mutated allele (17).

SI.1.4 Main treatment options

The principal aim of treating PWH is to treat and to prevent bleeding and subsequent end-stage haemophilic arthropathy (2) by replacement of the missing FVIII. The WFH has established that one international unit (IU) of FVIII clotting factor concentrate per capita is the target minimum needed for countries to achieve optimal survival in the haemophilia population (13). In the 2015 WFH Global Survey, the mean global FVIII usage was 2.20 IU per capita, with mean FVIII usage in Europe ranging from 0.001 IU per capita (based on humanitarian aid data) in Azerbaijan to 14,271 IU per capita in Denmark (10).

FVIII replacement therapy may be given in response to a bleed (episodic or on-demand treatment), or it may be given regularly to prevent bleeds (prophylactic therapy).
The effectiveness of prophylactic treatment is recognised in the WFH guidelines (2). A recent study also reported superior efficacy of prophylactic therapy compared with on-demand treatment in adults with severe haemophilia (18). However, prophylaxis is expensive, and its use varies in different countries. In the 2015 WFH Global Survey, the percentage of PWH under the age of 18 years receiving prophylactic treatment varied in Europe from 0% in Kyrgyzstan, Moldova and Ukraine to 100% in Denmark, Estonia, Germany, Hungary, Lithuania, Latvia and the Netherlands (10). In a study conducted by the European Haemophilia Therapy Standardisation Board (EHTSB), which represents 25 HTCs from 14 European countries, 76%–100% of children with haemophilia received prophylaxis at all of the included centres (19). The use of prophylaxis in adults with severe haemophilia was more variable. The percentage of adult patients with severe haemophilia receiving

prophylaxis was ≤50% at 62% of centres, 51%–75% at 28% of centres and 76%–100% at 10% of centres (19). In a study of Canadian adults with severe haemophilia A, 70% of participants were receiving prophylaxis, with older adults (>40 years of age) less likely to use prophylaxis than younger adults (58% *vs.* 75%) (20). Both plasma-derived (pdFVIII) and recombinant FVIII (rFVIII) concentrates are available. In 2010, 53% of all patients receiving FVIII products worldwide received rFVIII while 42% were treated with plasma-derived FVIII (pdFVIII) (13). In 2015, of the total IU administered worldwide, 31% was plasma-derived and 64% was recombinant (10). In European countries, the use of recombinant products as a percentage of total IU administered ranged from 0% in Macedonia, Moldova and Montenegro to 99% in Denmark. The United Kingdom Haemophilia Centre Doctors' Organization (UKHCDO) guideline recommends rFVIII as the treatment of choice (21) and 5 other European countries (Italy, the Netherlands, Norway, Poland and Spain) have a policy of prescribing recombinant concentrates in children with haemophilia (19).

Novel therapies are expected to reduce the need for clotting factors and by-passing agents in the treatment of patients with haemophilia with and without inhibitors. One of these non-replacement therapies, Emicizumab has been approved for prophylaxis of bleeding both for patients with and without FVIII inhibitors. It works by providing a bridge for factors IX and X to bind. It is not indicated for treatment of bleeds due to increased risk of thrombotic complications.

The arrival of gene therapy offers patients the possibility to reduce the burden of treatment for prophylaxis by eliminating the need for regular infusions with a long-term expression after a single infusion. Several viral serotypes as vectors for gene therapies are in development for haemophilia A, and currently one of them has been approved (Valoctogene Roxaparvovec [Roctavian]) by Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2023 (22). Valoctogene Roxaparvovec is an adeno-associated virus 5 (AAV5) -based gene-therapy vector containing a human coagulation FVIII complementary deoxyribonucleic acid (DNA) driven by a liver-selective promoter. Nevertheless, there are areas of uncertainty associated to gene-therapy, including the long-term duration of FVIII expression, variability on FVIII expression, potential immune-related hepatic adverse events, the need of steroids use at the start of treatment in some of the patients, limitations to receive an additional gene-therapy, and pre-existing neutralizing antibodies against vectors that could compromise efficacy and safety of gene-therapy (23).

Mortality and morbidity (natural history)

Mortality

Before the 1970s, the mean life expectancy of PWH was <30 years, and haemorrhage was the most common cause of death. In the 1960s, the availability of FVIII preparations led to improved life expectancy. However, the contamination of the plasms donor pool with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) between 1978 and 1985 meant the acquired immune deficiency syndrome (AIDS) became the leading cause of death. In addition, mortality from liver diseases, including liver cancer, substantially increased. The introduction of virus-inactivation techniques in the preparation of plasma-derived concentrates from 1984, as well as the production of recombinant factors since the late 1980s,

greatly improved the safety of replacement therapy (24, 25). The subsequent decline in HIV-related mortality in PWH was consistent with that seen in the general population, reflecting improvements in combined highly active anti-retroviral therapy (HAART). Since then, the lifespan of PWH has progressively approached that of men in the general population.

In a prospective cohort study in the Netherlands, (24), overall mortality was higher in PWHA and patients with haemophilia B (PWHB) compared with the general male population (standardised mortality ratio [SMR] 2.3; 95% confidence interval [CI] 1.9-2.8). In patients with severe haemophilia, life expectancy was 59 years in the study cohort followed between 1992 and 2001, but 63 years in a cohort followed retrospectively between 1972 and 1985. When virus-related deaths were excluded, life expectancy was calculated as 72 years and mortality was moderately higher than in the general Dutch male population. Acquired Immune Deficiency Syndrome (AIDS) was the main cause of death (26%) and 22% of deaths were due to HCV infection complications, of which liver cirrhosis was the most prevalent.

Another study evaluated 6,018 HIV-free men with haemophilia A or B registered in the UKHCDO database from 1977 to 1998, with follow-up until 01 JAN 2000 (26). Median life expectancy was 63 years with severe haemophilia and 75 years with moderate/mild haemophilia, compared with 78 years for the general male population. All-cause mortality in PWH exceeded mortality in the general population by a factor of 2.69 (95% CI 2.37–3.05). Mortality from bleeding, liver diseases or Hodgkin diseases was higher than mortality in the general population; however, for ischaemic heart disease it was lower, at 62% (95% CI 51-76%) of the rate for the general population.

Retrospective data from 443 Italian PWH who died between 1980 and 2007 showed that the SMR compared with the male Italian population decreased from 1.98 (95% CI 1.54-2.51) in 1990-1999 to 1.08 (95% CI 0.83-1.40) in 2000-2007 (25). During the latter period, mortality overlapped that of the general population. Similarly, life expectancy in the haemophiliac population increased from 64.0 years in 1990-1999 to 71.2 years in 2000-2007, approaching that of the general male population. Although HIV infection was the main cause of death (45%), 13% of deaths were caused by HCV-associated complications.

In a Swedish study of PWHA/B, the mean age at death increased from 58.8 years during 1981-1990 to 69.4 years during 2001-2008 (8). All-cause mortality was significantly higher for PWH than for matched controls (all severities of haemophilia: hazard ratio [HR] 2.2, 95% CI 1.8-2.7). For those with severe haemophilia, the most frequent cause of death was immunodeficiency (31%), followed by haemorrhage- and cerebrovascular-related death (23%) and malignancies (12%).

In the 2008/2009 Annual German Haemophilia Survey of 9,101 patients with bleeding disorders, nearly half of whom had haemophilia A (27), the all-cause mortality was 0.24% per year compared with 0.39% per year in the 2007/2008 reporting period. In the corresponding 2011/2012 survey, the all-cause mortality remained at 0.24% per year for the period 2010-2011 (28). Despite a decrease in HIV/AIDS mortality among PWH, HIV/HCV

co-infection seems to increase the risk of progression of severe liver disease and thus increase mortality.

There is conflicting data on the risk of death from cancer in PWH. A 2011 literature analysis of HIV-negative PWH showed a reduced cancer mortality risk (excluding HCV-related mortality) in the virally unaffected haemophilia population compared to the matched general male populations (3 relevant studies summarised in Table SI-5) (29). However, in 717 Dutch PWH (HIV or HCV status not reported), SMRs of 2.5 for neoplasm (95% Confidence Interval [CI] 1.4-4.2) and 8.6 for lung cancer (95% CI 3.1-18.7) were reported, indicating an excess of deaths from cancer in PWH compared with the general male population (30). Conversely, a cohort study using Taiwan's National Health Insurance Research Database found no difference in the survival rate between PWH and the general population with cancer, following diagnosis of the disease (31).

Table SI-5: SMRs of cancer in HIV-negative haemophilia A patients excluding HCV-related cancer

Reference	Location	Covered time	SMR (95% CI)
(32)	Canada	1980–1995	0.3 (0.1–0.7)
(26)	United Kingdom	1977–1999	0.90 (0.76–1.07)
(25)	Italy	1990–1999	0.34 (0.17–0.61)
		2000–2007	0.67 (0.38–1.09)

From (29).
CI: Confidence Interval; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; SMR: Standardized Mortality Ratio; %: Percent

In summary, the availability of FVIII treatment has reduced mortality among PWH. However, there was a period when blood products were contaminated with HCV and HIV, and subsequently AIDS replaced haemorrhage as the main cause of mortality. Overall life expectancies began to increase following the introduction of HAART therapy and coagulation factors free of viral infection.

Morbidity

In PWH, the majority of bleeding occurs internally into joints, especially those that are hinged (2). Cumulative joint bleeding episodes induce progressive degradation of joint structure and function with various degrees of chronic disability (33). Serious bleeds also occur in muscles and mucous membranes (2). Less frequently, life-threatening bleeds occur in or around vital areas or organs such as the gastrointestinal system or enclosed areas like the intracranial or intracerebral spaces (33). The approximate frequencies of bleeds by site are: joints (haemarthrosis), 70%-80%; muscle, 10%-20%; central nervous system, 5%-10%; bleeds at all other sites, <5% (2).

Infants and young children with haemophilia, especially those aged 0–2 years, have distinct bleeding patterns. Birth is the first haemostatic challenge (34). In the neonatal period, intracranial haemorrhage (ICH) is the most serious complication, resulting in potential lifelong consequences, but surgery-related bleeds, extra-cranial haemorrhages (ECH), and

bleeds from venepunctures are also common. Between 1 and 6 months of age, oral bleeding and head bleeding due to intercurrent injury are common events. Later, joint haemorrhages become more common (35). In a cohort of 508 children with haemophilia, born between 1990 and 2008 in 12 European HTCs, the incidence of major bleeds during the neonatal period (first 28 days after birth) was 4.7%, the incidence of head bleeds was 3.5% and the incidence of ICH was 0.8% (34). Forceps-/vacuum-assisted delivery was the only risk factor for neonatal head bleeding (odds ratio [OR] 8.84; 95% CI 3.05-25.61); mild haemophilia and maternal awareness of carrier status showed protective effects (OR 0.24; 95% CI 0.05-1.05 and OR 0.34; 95% CI 0.10-1.21, respectively) (34). In a UK-based cohort of 1,111 children with inherited bleeding disorders, 38 developed ICH, giving an overall risk of ICH of 3.4% (95% CI 2.5-4.7) (36). Of the 38 children with ICH, 27 developed ICH in the first year of life (18 in the neonatal period). Five (13%) of the children died from ICH, and the risk of significant motor disorder deficits among survivors of ICH was 56% (95% CI 39-72).
A recent meta-analysis found that the risks of ICH and ECH at birth were increased 44-fold (95% CI 34.7-57.1) and 8-fold (95% CI 5.4-12.6), respectively, in newborns with haemophilia compared with the general population (37). In newborns with haemophilia, the risk of ICH was increased in those who underwent an assisted vaginal delivery (OR 4.4; 95% CI 1.5-13.7) and decreased in those who were delivered by Caesarean section (OR 0.34; 95% CI 0.1-0.8) compared with those who underwent a vaginal delivery.

Haemarthroses begin in the toddler age. An inverse correlation between bleeding tendency and the endogenous FVIII level is reported, and preventive therapy in children is recommended. Two large, prospective, multicentre, randomised clinical trials in children (ESPRIT study and Joint Outcome Study [JOS]) showed that alternate day prophylaxis was clearly superior to enhanced episodic factor therapy (38). Primary prophylaxis should begin in the first 2-3 years of life before repeated haemarthrosis occurs. Prophylaxis started after the age of 6-7 years is unable to prevent progressive arthropathy (39). As demonstrated in the mentioned studies, prophylaxis decreases episodes of joint bleeds and chronic arthropathy, but effectiveness depends on prescription of prophylaxis and adherence to the prescribed regimen (40).

ICH remains one of the most severe bleeding complications for PWH into adulthood.
In a retrospective review of data from the Italian Association of Haemophilia Centres (*Associazione Italiana dei Centri Emofilia,* AICE), the overall annual rate of ICH was 2.50 events per 1,000 patients (95% CI 1.90-3.31) (41). The risk of ICH was highest among the youngest children but increased again after the age of 40 years. The most common symptoms at presentation were headache (45.5%), coma (27.6%) and vomiting (27.6%). Major neurological sequelae were reported for 22.7% of patients; 25% of patients died.

Joint damage increases with increasing age in both patients with moderate and severe haemophilia, with more than half of PWH aged ≥65 years reported to have severe damage in all of the 6 joints most commonly affected by bleeding (42, 43). There was also a high incidence of joint instability and balance dysfunction. Orthopaedic operations are often required to reduce pain and disability associated with haemophilic arthropathy when

conservative approaches are unsuccessful (44). Arthropathy is also associated with reduced bone mineral density (BMD) in severe haemophilia.

In summary, in PWH, most haemorrhages occur internally into joints and muscles. Haemarthrosis results in joint damage, the most common morbidity in this patient population. The risk of life-threatening bleeds, such as ICH, begins at birth and persists into adulthood.

SI.1.5 Concomitant medication(s) in the target population

Anti-fibrinolytic drugs may be used as adjunctive therapy in PWH, for example during dental extractions (2).

Acute and chronic pain (including pain resulting from internal bleeding, chronic arthropathy or surgery), are common in PWH. Pain management involves paracetamol or, if this is not effective, cyclooxygenase-2 (COX-2) inhibitors, a combination of paracetamol with either codeine or tramadol, or morphine (2). In a survey of patients with severe haemophilia in the UK, more than half of patients had used over-the-counter analgesics in the last month and over a third had been treated with prescription analgesics (45). In a US survey of 764 PWH, medications used for the management of acute pain included short-acting opioids (55%), paracetamol (53%), non-steroidal anti-inflammatory drugs (NSAIDs) (36%), long-acting opioids (21%) and non-opioid medications (7%) (46). The medications reported to be used for the treatment of persistent pain included short-acting opioids (48%), paracetamol (46%), NSAIDs (36%), long-acting opioids (24%) and non-opioids (1%). The high rate of NSAID use is notable; current WFH guidelines recommend avoiding NSAIDs, except for certain COX-2 inhibitors (2). The proportion of patients using COX-2 inhibitors was not reported in the US survey (46).

The prevalence of HIV and HCV, and therefore the use of HAART and HCV antiviral treatment, remains significant among adults with haemophilia born before the availability of virally-inactivated and recombinant factor concentrate products (44). In PWH who develop osteoporosis, treatment may include oral vitamin D and oral calcium, parathyroid hormone, selective oestrogen receptor modulators (SERMs) or bisphosphonates (47). New drugs emerging for the treatment for osteoporosis, such as denosumab, ronacaleret and odanacatib, may also play a role in the management of this condition in PWH although clinical studies in this patient population are warranted (47).

The management of acute coronary syndromes (ACSs) in PWH may involve concomitant treatment with unfractionated heparin, aspirin and dual anti-platelet therapy whereas the development of atrial fibrillation may necessitate the use of low dose aspirin or vitamin K antagonists (48). Data on the efficacy and safety of these therapies is lacking in PWH; therefore, during co-administration of these antithrombotic treatments, adjusting the schedules of factor replacement therapy and monitoring of plasma levels of FVIII is essential (48). PWH are twice as likely to have hypertension compared with the general population and therefore more commonly use anti-hypertensive medications (2).

PWH and cancer may be treated with invasive or surgical procedures and/or chemotherapy and radiotherapy. In a retrospective study of data from Italian haemophilia centres on 122 patients with 127 cancers, haemorrhagic complications were more common with

chemotherapy (14%) and radiotherapy (19%) than with invasive or surgical procedures (8% and 0.2%, respectively) (49).

SI.1.6 Important co-morbidities found in the target population

Co-morbidities in the target population are influenced by 1) sequelae of the disease, 2) sequelae of its treatment, and 3) ageing process of the population occurring as a consequence of prolonged survival. Arthropathy is the most common co-morbidity affecting PWHA. Other frequently observed co-morbidities in PWH are HIV and HCV infections transmitted by blood products patients received in the past for haemophilia treatment. These diseases are mainly present in the adult haemophilia population since viral elimination methods were introduced in response to disease transmission outbreaks in the 1980s. Furthermore, owing to the increased life expectancy, age-related co-morbidities such as cardiovascular diseases (CVDs) and cancers are becoming a more common occurrence in PWH.

Table SI-6: Haemophilia related co-morbidities

Haemophilic arthropathy	Joint bleeding accounts for more than 90% of all serious bleeding events in patients with severe haemophilia and remains the leading cause of morbidity. It leads to chondrocyte apoptosis, inhibition of cartilage-based proteoglycan synthesis, and induction of chronic synovitis and therefore plays an important role in the aetiology of degenerative joint disease (50, 51). Over time, repeated bleeding into a “target” joint leads to the development of irreversible arthropathies associated with pain, muscle atrophy, deformity and disability. Several authors highlight the need for a timely control of bleeding episodes to minimise joint damage and thereby preserve musculoskeletal function and improve patient quality of life (51-54). Joint preservation procedures may help to slow joint damage in children with haemophilia (55). This co-morbidity appears to be related to insufficient factor VIII (FVIII) replacement therapy, both quantitative (annual dose) and qualitative (need for regular, long-term prophylaxis) (56). In addition, the risk of arthropathy is increased in the presence of FVIII inhibitors (57). Debilitating haemophilic arthropathy develops at a young age, reflected by the average age of patients undergoing total knee replacement surgery of 36–39 years (58, 59). Patients born in the 1950s, before introduction of coagulation factor concentrates (CFC), will have 4 to 6 arthropathic joints. In a recent Canadian cohort study, 23% of older adults (≥40 years) had at least 4 arthropathic joints, compared with 5% of younger adults (20). In a retrospective study of 146 patients with moderate/severe haemophilia in Taiwan, the prevalence of haemophilic arthropathy was 42.8%, 64.3%, 97.1%, 93.1%, 100% and 100% in patients aged 4–10 years, 11–19 years, 20–29 years, 30-39 years, 40–49 years and ≥50 years, respectively (60). Most of the physical, psychosocial, and financial disabilities in patients with severe haemophilia A are caused by the effects of recurrent hemarthrosis and chronic arthritis. The management of advanced stages of haemophilic arthropathy consists of physiotherapy and regular exercise; this can prevent falls, osteoporotic fractures and immobilisation (61, 62). Secondary to joint and/or muscle bleeding, hip abnormalities have been reported in 16.7% of patients with haemophilia A (PWHA) and patients with

Table SI-6: Haemophilia related co-morbidities

	haemophilia A (PWHB) (63). Independent risk factors for hip abnormalities included haemophilia A disease type, severe haemophilia disease status and concomitant ankle arthropathy. Summary: Arthropathy is one of the most common co-morbidities found in patients with haemophilia (PWH) and can have a severe impact on quality of life.
Osteoporosis	Adults with haemophilia show an increased risk of developing low bone mineral density (BMD) (47, 64, 65). Low bone mass (osteopenia and osteoporosis combined) has been reported in 22–84% of PWH (47). One explanation for this may be limited physical activity during childhood and adolescence because of the risk of bleeding and pain related to haemophilic arthropathy (64-67). In addition, various interactions have been described between coagulation and bone structure/metabolism (68) (69, 70). Ranta *et al.* (2011) found an increased urinary calcium loss and altered bone metabolism in PWH that over time may contribute to osteoporosis (71). A further risk factor is vitamin D deficiency. A recent Turkish cohort study noted a high prevalence (96%) of vitamin D deficiency in children with haemophilia, suggesting a need to monitor the vitamin D status of these patients in other regions (72). In a study by Naderi *et al.* (2012), mean body mass index (BMI), number of arthropathic joints and the number of joint bleeding episodes in the previous year were significantly higher in patients with osteoporosis than in patients with osteopenia or normal BMD (73). The mean dose of coagulation factor administered, the number of joint bleeding episodes in the previous year, and the number of arthropathic joints were all significant independent predictors of spinal and femoral BMD. A meta-analysis performed by Iorio *et al.* confirmed the association between low BMD and severe haemophilia. Lumbar BMD was significantly lower in patients with severe haemophilia than in controls, both in adults and children (in adults, pooled standardised mean difference [SMD] −1.379, 95% confidence interval [CI] −2.355 to −0.403, $p = 0.006$; in children, pooled SMD −0.438, 95% CI −0.686 to −0.189, $p = 0.001$) (74). Khawaji *et al.* concluded from their studies that the long-term use of FVIII prophylaxis from early childhood onwards may preserve normal BMD even in patients with severe haemophilia and prevent the development of osteoporosis in older age (75). Physical training can also have a positive impact on BMD (67). This may explain why some authors could not find a difference in BMD between adult patients with severe and mild haemophilia (75, 76). Summary: Adults with haemophilia are more likely to develop reduced BMD compared with matched controls, which may be in part due to reduced physical activity during childhood. There is no clear consensus regarding the risk factors for reduced BMD in PWH.
Chronic hepatitis C infection	Chronic hepatitis C infection is a major co-morbidity and a leading cause of mortality in PWH. Before the introduction of adequate viral inactivation methods for hepatitis C virus (HCV) in 1992, 98% of patients treated with large pool products and 66% of patients treated with cryoprecipitate were infected with HCV. More than 80% of these patients developed chronic HCV, which may cause liver fibrosis, progressing to cirrhosis (77), or hepatocellular carcinoma (HCC), which has become an increasingly important cause of death as overall life expectancy has increased (78). An analysis of an Australian

Table SI-6: Haemophilia related co-morbidities

	bleeding disorders population reported the prevalence of HCV at 94% and 52% in patients with severe and mild haemophilia A, respectively (79). A recent analysis of United States (US) discharge data reported a lower prevalence of HCV in PWH (30.5%), but this remained higher than the prevalence of HCV in patients without haemophilia (2.8%) (80). A US database analysis of 4,899 PWH reported the prevalence of HCV in patients with severe haemophilia as 92.3%, 93.0%, 84.4% and 32.6% in those born before 1958 and during 1958-1975, 1976–1982 and 1983–1992, respectively; the corresponding percentages in patients with mild haemophilia were 54.2%, 64.6%, 33.3% and 6.2%, respectively (81). In a cohort of 847 PWH infected with HCV, there was a cumulative incidence of end-stage liver disease (ESLD) of 11.5% after 35 years of infection and a cumulative incidence of ESLD of 35.1% in HIV co-infected patients (77). A more recent study showed a similar cumulative incidence of ESLD in patients with haemophilia or von Willebrand disease infected with HCV (12.3% after 40 years of infection) (82). A study from 2011 showed that HCV-seropositive men with a HIV co-infection had significantly higher mean Metavir fibrosis scores than HCV-mono-infected patients (83). In addition, a multivariate analysis of data from haemophilia treatment centres (HTCs) (77) demonstrated that in all HCV-antibody-positive patients with congenital bleeding disorders, the risk of ESLD was increased with human immunodeficiency virus (HIV) infection (hazards ratio [HR], 13.8; 95% CI 7.5-25.3). Older age at the time of infection (HR, 2.3/10 years; 95% CI 2.0-2.8) was also associated with a higher risk of ESLD (77, 84). Indeed, the incidence of ESLD in PWH may be as high as 5-10% (85). The HCV therapy historically consisted of a combination of PEGylated interferon (IFN) and ribavirin. Success rates of treatment varied from 40% to 90% depending on the HCV genotype (56). Sustained virological response was reported in 41% of patients with inherited bleeding disorders in a retrospective study in Sweden (86) and in 33%, 58% and 93% of patients with haemophilia or von Willebrand disease in 1990–2001, 2002–2011 and 2012 onwards (when directly acting antiviral agents became available), respectively, in a US-based study (82). Recently, several direct-acting antiviral agents have been developed that in combination can interrupt HCV replication with higher and sustained virological responses (e.g., Sofosbuvir/Velpatasvir or Glecaprevir/Pibrentasvir) (87). Summary: Before the widespread introduction of modern production methods for coagulation factors, many patients were infected with HCV. As a result, there is a high prevalence of liver fibrosis and cirrhosis among PWH, which may progress to ESLD.
HIV infection	PWH treated with plasma-derived CFC were exposed to HIV between 1978 and 1986. HIV infection rates vary considerably among countries. In the USA, new infections from contaminated blood products were rare after 1987 but by this time 50% of PWH were seropositive for HIV (88). A US database analysis of 4,899 PWH reported the prevalence of HIV in patients with severe haemophilia as 42.9%, 61.0%, 26.2% and 1.0% in those born before 1958 and during 1958–1975, 1976–1982 and 1983–1992, respectively; the corresponding percentages in patients with mild haemophilia were 4.7%, 11.9%, 4.0% and 0.2%, respectively (81). In a Swedish study, the proportion of PWH with an International Code for Diseases (ICD) for HIV infection was 7%

Table SI-6: Haemophilia related co-morbidities

	(8). The prevalence of HIV infection was higher in PWH than in patients without haemophilia in a recent analysis of US discharge data (13.7% vs. 1.2%) (80). However, according to national yearly surveys in Finland between 1985 and 1989, only 1% of patients with bleeding disorders had antibodies for HIV (89). Many patients died of HIV/AIDS before the introduction of highly active anti-retroviral therapy (HAART) in 1996. Most HAART regimens consist of nucleoside reverse-transcriptase inhibitors (NRTIs) combined with a non-nucleoside analogue (Non-Nucleoside Reverse Transcriptase Inhibitor, NNRTI) or a protease inhibitor (PI). An increased incidence of myocardial infarction has been reported in association with PI use in patients infected with HIV (90). The use of PIs in PWH has been reported to increase the risk of bleeding (56). In a retrospective analysis of the medical records of 67 patients with hereditary bleeding disorders who were HIV positive, 51% developed an increased bleeding tendency when administered PI therapy (91). Approximately 80% of men with haemophilia and HCV infection became co-infected with HIV, which was shown to accelerate HCV-related liver disease, leading to a higher HCV viral load and a nearly four-fold greater rate of liver disease progression than in those with HCV alone. Data from a cohort of men with haemophilia and HCV infection demonstrated that ESLD-free survival in co-infected men was significantly improved with HAART (83). Indeed, the rates of liver disease progression in such patients were similar to those in HCV mono-infected men. Summary: In some regions, a high proportion of PWH were exposed to HIV through contaminated blood products, and HCV co-infection was commonplace. The use of PIs, a component of HAART treatment, may increase the risk of bleeding in PWH.
Infections of central venous access device (CVAD)	In a study of fifty-nine patients with a total of 97,936 (median 1,768 days per patient) CVAD days, the median age at CVAD placement was 2.7 years (range 0–14.0). Twenty-six (44%) patients reported CVAD infections during the study period from JAN 1993 to OCT 2000. Twenty-four patients had their CVAD replaced, 17 (71%) of whom reported having infections and 7 (29%) of whom had a history of inhibitor. The strongest predictor for having any infections was inhibitor status, although no risk factors had statistically significant effects. Among the 26 patients reporting infections, 42% had more than one CVAD-related infection. Seven patients had multiple infections involving the same organism. The mean rate of infection was 0.45 per 1,000 catheter days (95% CI, 0.33–0.60.) Those with a history of inhibitor had an infection rate of 0.66 compared with 0.38 per 1,000 catheter days (P=0.09) for those without a history of inhibitor. Patients who were older (greater than the median age of 2.7) at CVAD placement had a lower rate of infection (0.29 *vs*. 0.65, P<0.01) compared with those < or = 2.7 years (92). Data from the Study for the Prevention of Joint Disease in Preschool Children with Severe Haemophilia, a randomised clinical trial of prophylaxis versus episodic therapy, evaluated the association between CVAD-related infection and treatment. The crude and adjusted rate ratios for first CVAD-related infection per 1,000 CVAD days associated with episodic therapy *versus* prophylaxis were 1.42 (95% CI 0.46-4.40) and 1.23 (95% CI, 0.33-4.56), respectively, suggesting that prophylaxis likely does not put children at higher risk of CVAD-related infection than episodic therapy (93).

Table SI-7: Non-haemophilia-related co-morbidities

Cardiovascular disease (CVD)	Some studies have suggested that haemophilia protects against CVD mortality (56). According to a Dutch study performed between 1992 and 2001, age- and calendar-period-adjusted mortality caused by diseases of the circulatory system (including ischaemic heart disease and cerebrovascular disease) was lower in patients with haemophilia (PWH) than in the general male population in the Netherlands (17% *vs.* 28%). In another study, the standardised mortality ratio (SMR) for ischaemic heart disease in PWH compared with the general male population was 0.5 (95% confidence interval [CI] 0.2–1.1) (24). Likewise, a SMR of 0.62 (95% CI 0.51-0.76) for ischaemic heart disease was observed by Darby *et al.* (2007) in a United Kingdom (UK) cohort of non-human immunodeficiency virus (HIV) infected PWH (26). The frequency of deaths from ischaemic heart disease was lower than expected in Dutch PWH (30). Similarly, in a Swedish study, a significantly lower proportion of PWH died from ischaemic heart disease (12%) than matched controls (29%; p <0.001) (8). This lower mortality rate from ischaemic heart disease has been attributed to the hypocoagulable state in haemophilia which might provide protection against thrombus formation (94). Despite these findings, data from other studies show that the prevalence of cardiovascular risk factors in older PWH is comparable to that in the general population. For example, Foley *et al.* (2010) reported that the prevalence of risk factors and the degree of coronary luminal stenosis were similar in PWH and controls (95). Biere-Rafi *et al.* (2011) found no significant difference in the prevalence of up to four cardiovascular risk factors between adult PWH and age-matched male controls (96). In fact, the 10-year cardiovascular mortality risk was similar for PWH and for the age-matched general population. In addition, the study showed that mean total cholesterol levels and mean low-density lipoprotein (LDL)-cholesterol levels were lower in PWH than in control subjects (96). Another study by Sharathkumar *et al.* (2011), conducted in a treatment centre in the United States of America (USA), also reported that the prevalence of risk factors for CVDs among PWH was similar to those of age-matched general US non-Hispanic white males (97). In the study by Huang *et al.* (2015), the frequency of risk factors, including hypertension and hyperlipidaemia, was lower in PWH compared with the general population. Notably, the estimation of cardiovascular risk in PWH may be subject to methodological bias and therefore not predictive of cardiovascular mortality in this patient group (98). In recent studies, and as more PWH are surviving to old age, ischaemic CVDs is increasingly diagnosed among them, and it is likely that this CVD burden, among PWH, will continue to increase (99). CVD events were reported in 8.2% of 294 Canadian PWH aged ≥ 35 years during a mean follow-up of 5.9 years; the median age at event in these patients was 63 years (range: 46–83) (100). Coronary artery disease was reported in German PWH aged ≥ 60 years, albeit at a reduced prevalence when compared with published data from the German general population (60–69 years: 8.1% *vs.*19.5%; 70–79 years: 11.8% *vs*. 30.5%) (101). By contrast, Sharathkumar *et al.* (2011) reported that the prevalence of coronary artery disease, stroke, and myocardial infarction was about two-fold higher in PWH compared with US non-Hispanic white males, and concluded that strategies for CVD prevention are needed for PWH (97). A close co-operation between cardiologists and haematologists has been

recommended for the successful management of CVD in PWH (48, 102). Notably, in a 10-year retrospective study of adults with haemophilia, 25% of patients who experienced an acute coronary syndrome (ACS) event required modification of the initial ACS management protocol owing to the bleeding disorder (103).

The primary focus of a retrospective chart review published in 2011 by Khleif *et al.* was to identify and estimate the prevalence of co-morbid CVD in middle-aged and elderly patients with haemophilia A (PWHA) and patients with haemophilia B (PWHB) (71.4% and 28.6% of the study population, respectively) compared with age-matched male controls (104).

Over three quarters (78%) of PWH had at least one cardiovascular risk factor (hypertension, high cholesterol, diabetes mellitus, and overweight/obesity). The prevalence of CVD among PWH aged 40–59 years and ≥ 60 years (40.4% and 68.8%, respectively) was similar to that in the general US population aged 40-59 years and ≥60 years (39.1% and 71.3%, respectively). However, only 63 patients were included in this cohort, thus making it difficult to provide any statistically significant comparisons between the haemophilia study population and the general US male population (104).

Hypertension: Hypertension increases the risk of intracranial bleeding and myocardial infarction (56, 105, 106).

In the study by Khleif *et al.* (2011), the prevalence of hypertension was lower in the PWH study population compared to the US population except among patients aged 55-64 years and >75 years (45–54 years: 30.4% *vs*. 36.2%, 55-64 years: 53% *vs*. 50.2%, 65–74 years: 60% *vs*. 64.1%, >75 years: 100% *vs*. 65%) (104). Similarly, Huang *et al.* (2015) observed a decreased prevalence of hypertension in PWH compared with controls in a cohort of patients with cancer (32.6% and 41.6% in PWH and controls, respectively) (31). The prevalence of hypertension was also lower in PWH than in patients without haemophilia in an analysis of US discharge data (39.5% *vs*. 56.3%) (80). By contrast, another study reported PWH to have a higher mean blood pressure and to be twice as likely to have hypertension compared with the general population (2). Similarly, hypertension was more common in a cohort of Dutch and British PWH than in the general population (49% *vs*. 40%) (107). German PWH aged 50–59 years also showed an increased prevalence of hypertension when compared with published data from the German general population (52% *vs.* 42%) (101). A US-based retrospective study found that median systolic and diastolic blood pressure were increased in PWH compared with the general male population, particularly in adults aged <30 years (108). A European study of 532 PWH identified age and body mass index (BMI) as major risk factors for hypertension, similar to the general population (109). However, BMI and other well-known cardiovascular risk factors (renal function, cholesterol, smoking, diabetes, hepatitis C and race) do not appear to explain the increased prevalence of hypertension in PWH compared with the general male population (108).

Obesity: In addition to an increase in CVD risk, increased body weight can cause damage to already deteriorating joints in PWH. According to the results of a US-based study by Khleif *et al.* (2011), the prevalence of a BMI ≥25 kg/m^2 and ≥30 kg/m^2 was lower in haemophiliacs compared to the general population for all age groups (104). The prevalence of a BMI ≥35 kg/m^2 and ≥40 kg/m^2 was slightly increased in PWH compared to the general population. While over 65% of this US-based cohort were overweight or obese (BMI ≥25 kg/m^2 and BMI ≥30 kg/m^2, respectively), these rates were lower than in the age-matched

population. In addition, the proportion of patients with a BMI ≥25 kg/m^2 was higher among patients with mild haemophilia (72%) than among the age-matched population (104). In a Dutch and British cohort study, the prevalence of obesity was lower in PWH than in the general population (107). The prevalence of obesity was also lower in PWH than in patients without haemophilia in an analysis of US discharge data (5.2% *vs*. 9.0%) (80).

Hypercholesterolemia: Haemophilia is considered to be associated with low cholesterol levels compared with the general population (96), but the published literature is not fully conclusive. Hofstede *et al.* (2008) found no differences in the prevalence of high cholesterol between the haemophiliac population and the age-matched population (110). Conversely, in their retrospective chart review, Khleif *et al.* (2011) reported that PWH showed a markedly lower prevalence of high cholesterol than the normal US population (45–54 years: 17.4% *vs.* 36.2%, 55–64 years: 13.3% *vs.* 50.2%, 65–74 years: 20% *vs.* 64.1%, >75 years: 50% *vs*. 65%) (104). A retrospective case-control study in Taiwan reported similar results: the prevalence of hypercholesterolaemia was 4.7% in PWH *vs.* 17.4% in controls. The prevalence of hyperlipidaemia was also lower in PWH than in patients without haemophilia in an analysis of US discharge data (13.3% *vs*. 30.9%) (80).

Atherosclerotic Heart disease (ASHD): In a recent study on the effects of haemophilia and obesity on atherosclerosis, no differences in mean carotid intima-media thickness (IMT) and femoral IMT were observed between PWHA who were obese compared with obese controls (111). An atherosclerotic plaque was detected in 35% of obese PWH and 29% of obese controls (p = 0.49). It was concluded that the development of atherosclerosis in obese PWHA is similar to that in the general population highlighting the need for detection and treatment of cardiovascular risk factors in these patients (111).

In another study, the presence of atherosclerosis was evaluated in 69 PWH (median age, 52 years) by measuring coronary artery calcifications score (CACS) and carotid IMT. The median CACS in all patients was 35 (interquartile range [IQR] 0-110) and the geometric mean IMT was 0.80 mm (95% CI 0.76-0.84). The extent of atherosclerosis was in accordance with the normal age-dependent reference values for both measures, related to the traditional cardiovascular risk factors and was independent of haemophilia type and severity (112).

A study of hospital discharge data in Pennsylvania for the period 2001–2006 assessed the prevalence of ASHD (myocardial infarction, angina, and coronary disease), cardiac catheterisation, coronary angiography, co-morbidities and in-hospital mortality (113). PWHA with ASHD were older than PWHA without ASHD. This reflects the increased CVD risk with increasing age in the haemophiliac population as well as the increased risk of hypertension, hyperlipidaemia and diabetes. Patients with ASHD with and without haemophilia A had similar rates of hypertension (52.7% *vs.* 56.2%; p = 0.54), diabetes (28.4% *vs.* 27.1%; p = 0.80), and obesity (4.1% *vs.* 4.6%; p = 1.0). Ragni and Moore (2011) also reported that rates of ischaemic heart disease were similar in patients with ASHD with and without haemophilia A. In addition, PWH with ASHD showed similar cardiovascular risk factors, diagnoses at admittance to hospital, severity of illness and in-hospital mortality as the general population (113). However, a more recent analysis of US discharge data found that the prevalence of ASHD was lower in PWH than in patients without haemophilia (12.0% *vs*. 27.7%) (80).

The prevalence of atherothrombotic events were also found to be similar in

Table SI-7: Non-haemophilia-related co-morbidities

	PWH and the general population in a retrospective case-control study in Taiwan (114). However, the mean age at diagnosis of an atherothrombotic event was lower in PWH (49.0 years) than in the general population (55.8 years) in this study. Thrombosis: A recognised risk factor for venous thromboembolic complications is a high level of FVIII. A systematic review of published data on thrombotic adverse events (AEs) with FVIII/FIX concentrates used for the treatment of haemophilia (A and B) and von Willebrand disease was carried out on behalf of the EUropean HAemophilia Safety Surveillance (EUHASS) (115). According to this review, thrombotic AEs after clotting factor concentrate administration occurred rarely between 1990 and 2011. The overall prevalence of thrombotic events was 3.6/1,000 patients and 1.13/10,000 infusions. Among 4,420 PWHA (analysed throughout 45 studies) only 2 minor thromboembolic events (thrombophlebitis) were reported. Thromboembolic events after administration of FVIII in PWHA accounted for 0.045% of the 4,420 analysed patients, for 0.0002% of the total number of infusions and for 0.47% of the total number of AEs. A retrospective study of PWH undergoing joint replacement surgery showed that thromboprophylactic therapies could be omitted in this patient population without an increased risk of venous thromboembolism (116).These findings support the low risk of thrombosis in PWH treated with FVIII concentrate. Emicizumab (non-factor replacement therapy) is associated with an increased risk of thrombosis and thrombotic microangiopathy (TMA), in combination with aPCC. Patients receiving Hemlibra prophylaxis should be monitored for the development of TMA and thromboembolism when administering aPCC. Summary: It is plausible that PWH, who experience a hypocoagulable state, may be at a reduced risk of thrombus formation and development of CVD. Some studies have suggested that PWH have a reduced risk of CVD compared with the general population. Nevertheless, despite of a potentially lower rate of CVD, cardiovascular events do occur in PWH and very high or more than normal FVIII levels can be a potential risk factor.
Malignancy	Liver cancer and non-Hodgkin lymphoma are the most prevalent malignancies in PWH infected with hepatitis C virus (HCV) or HIV. Indeed, the increased risk of HCC in adult PWH overall can be considered a direct consequence of the high prevalence of chronic HCV infections in this population resulting from infection with HCV and HIV *via* contaminated haemophilia blood products in the 1970s to 1985 (84). A retrospective study from the Italian Association of Haemophilia Centre (*Associazione Italiana dei Centri* Emofilia, AICE) examined the association of cancer and concomitant infections with HCV or HIV in PWH (49). Analysis of 122 PWH with coincident cancer showed that 83% also had a HCV infection and that 43% of the cancer cases were assessed to be HCV-related. Among PWH with cancer, 22% had a concomitant HIV infection, and 9% of the cancer cases were assessed to be HIV-related. Virus-related cancers were more frequent in patients with severe haemophilia than in patients with mild/ moderate forms. Within the study period 1980-2010, 69% of cancer cases were reported in the decade from 2001 to 2010 (49). This may be explained by the increased survival among PWH and the long-time typically required for

cancer development.

While haemostasis has been associated with cancer development (29), it is unclear as to whether PWH have an increased incidence of non-virus-related cancers, as well as whether their survival rates differ to those of the general population. Some published data suggest a similar incidence and outcome of cancers overall in PWH and the general population. Several studies have reported that, with the exception of HCV-related hepatocellular carcinoma (HCC), mortality rates for cancer are the same in PWH compared with the general population (24, 26, 117). In a recent study, the prevalence of malignancies was analysed in a total of 3,510 PWH (118). The age- and race-adjusted rates of leukaemia, lymphoma and liver cancer were significantly higher among PWH than among the male population in the USA (prevalence ratio 3.1 [95% CI, 1.4–7.0], 2.9 [95% CI 1.8–4.6] and 44.6 [95% CI 19.1-103.8], respectively), whereas the prevalence of prostate cancer was lower in PWH compared with the general population. However, overall, the prevalence of most cancers was similar in males with and without haemophilia.

Other studies have reported conflicting data on the incidence of non-HCV and HIV-related malignancies in PWH. One Dutch study found an excess of death from cancers, particularly lung cancer, in PWH and a German study found an almost four-fold increase in extra-hepatic malignancies in PWH compared with the general population (30, 119). Two analyses of an Asian population reported a higher incidence of non-virus-related cancers amongst PWH, compared with the general population (31, 120). A recent Swedish study of 1,431 PWH and 7,150 matched controls also found a significantly increased incidence of cancer (primarily haematologic malignancies and cancer in urinary organs) in PWH *vs.* controls, and showed that this difference was independent of HIV infection or viral hepatitis (121). These findings contrast with several other studies that found no significant increase in malignancy in non-HIV and non-HCV-infected PWH (reviewed by (122)). Notably, in the analysis by Huang *et al.* (31) (2015). PWH with cancer were younger but had similar survival rates to people with cancer in the general population.

In 2010, Dunn conducted a 42-year retrospective literature review of cancer in PWH (123). Thirty-two cases of leukaemia and 159 malignant solid tumours (non-Kaposi's sarcoma, lymphoma or HCC) were identified. Age ranged from 8 months to 40 years. In 20 patients, leukaemia types could be identified: two patients had chronic myeloid leukaemia, eleven had acute lymphocytic anaemia, and seven manifested acute myeloid leukaemia. Most were HIV-negative, or the HIV-status was not reported. The patients with leukaemia tended to be younger than those with solid tumours.

When chemotherapy, radiotherapy, or any invasive procedures are performed to treat cancer in haemophiliac patients, increased bleeding risk should be taken into account. Haemorrhagic complications were reported to occur in 14% of patients undergoing chemotherapy and in 19% of patients with radiotherapy (49). The use of routine procedures for general health maintenance in the elderly (e.g., colonoscopy) can be more complex in PWH due to the inherent risk of bleeding, and serious disorders such as malignancy can be overlooked if signs of abnormal bleeding are attributed to haemophilia rather than to cancer (78).

Summary: With a high prevalence of HIV or chronic HCV infection among PWH, the rates of virus-associated cancers are high in PWH. It remains unclear whether the rates of malignancies in PWH are elevated compared with

Table SI-7: Non-haemophilia-related co-morbidities

	the general population.
Other diseases	Renal disease: It has been suggested that elderly PWH may be at greater risk of developing acute or chronic renal disease than the general population (122). A study of children with haemophilia identified a predisposition to hypercalciuria in this patient group, which may predispose them to renal disease in adulthood (124). By contrast, in a 14-year cohort study of patients with cancer, PWH had a lower prevalence of chronic kidney disease (CKD) compared with controls (4.7% *vs.* 7.9%) (31). Similarly, in a cohort of adult males with mild to severe haemophilia hypertension, despite high prevalence of hypertension and haematuria, renal disease was rare and haematuria was not associated with a diagnosis of hypertension or renal dysfunction (125). HIV infection, hypertension, concomitant viral infections, exposure to nephrotoxic antiviral therapy, and frequent haematuria leading to structural abnormalities are factors likely to be associated with the pathogenesis of renal disease in PWH. The occurrence of intra-parenchymal haemorrhages in the kidneys of PWH possibly leading to hypertension has also been suggested (96). General co-morbidity associated with ageing: Older PWH face many challenges related not only to haemophilia but also to common co-morbidities associated with ageing. PWH often have known risk factors for CVD disease, such as hypertension, which could possibly counteract any protective effects bestowed by the hypocoagulable state. Dental disease: The oral health of PWH has not been extensively investigated, and the available evidence is contradictory. Inflammatory lesions of the apex of the tooth (apical periodontitis), caused by bacterial infection of the pulp, are visible radiographically as radiolucent periapical lesions (RPLs) (126). The frequency of RPLs in one or more teeth was significantly higher in PWHA, haemophilia B or von Willebrand's disease (67.2%) than in controls (48.3%). Despite this, patients with inherited coagulation disorders had a significantly lower frequency of root canal treatment for the condition (34.5%) than control patients (65.5%). In a recent case-control study, overall dental health did not differ between PWH and controls, although children with haemophilia had fewer caries in deciduous teeth compared with healthy children (127). Summary: As the life expectancy of PWH approaches that of matched controls, the prevalence of co-morbidities associated with ageing will be expected to rise.

ASHD: Atherosclerotic Heart disease; AICE: Association of Haemophilia Centres, BMD: Bone Mineral Density; BMI: Body Mass Index; CI: Confidence Interval; CACS: Coronary Artery Calcifications Score; CFC: Coagulation Factor Concentrates; CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease; ESLD: End-Stage Liver Disease; EUHASS: European Haemophilia Safety Surveillance; ; HAART: Highly Active Anti-Retroviral Therapy; HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; ICD: International Code for Diseases ; IMT: Intima-Media Thickness; IQR: Interquartile; LDL: Low-Density Lipoprotein; NRTI: Nucleoside Reverse-Transcriptase Inhibitor; SMR: Standardized Mortality Ratio; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; p: Probability; PI: Protease Inhibitor; PWHA: Patients with Haemophilia A; PWHB Patients with Haemophilia B; PWH: Patients with Haemophilia; RPL: Radiolucent Periapical Lesion; SMD: Standardized Mean Difference; %: Percent; US(A): United States (of America); *vs.*: Versus.

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

Table SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Single dose toxicity	
Jivi	
Systemic single dose intravenous toxicity studies were conducted in male Sprague Dawley rats [SN A47966] and in male New Zealand White rabbits [SN T1079870] to evaluate the effects of high doses (800 and 4000 IU/kg) of Jivi. BAY 14-2222 was used as a reference compound. Additional animals were treated on day 1 followed by a 2-week recovery period. Parameters evaluated include haematology, clinical chemistry, coagulation, and gross and microscopic pathology. No adverse effects were seen up to the highest dose of 4,000 IU/kg in either species; specifically, no thrombus formation or thrombus-related effects were observed. Therefore, the no observed adverse effect level (NOAEL) for these studies was 4,000 IU/kg for both Jivi and BAY 14-2222, which is approximately 67 times the highest clinical dose of 60 IU/kg.	High dose acute toxicity studies do not indicate any risk of thrombogenicity for human use.
Polyethylene glycol (PEG)-60 (BAY 1025662)	
Extended high single dose toxicity studies evaluated the acute toxicity of BAY 1025662, [SN PH-38066] (PEG-60-Maleimide-Cysteine, the PEG -maleimide component of Jivi) SNA48160 in male rats and rabbits. The effects of BAY 1025662 were assessed over an observation period of 2 weeks by clinical parameters, biochemistry, haematology, coagulation parameters and urinalysis, as well as determination of liver enzyme activity and full post-mortem examination. A single intravenous administration of BAY 1025662 was well tolerated up to the highest test dose of 210 mg/kg in the rat and 20 mg/kg in rabbits without any adverse findings. Based on the literature on PEGylated pharmaceutical products, no additional toxicity is expected from PEG in Jivi. In the acute PEG toxicity studies, the BAY 1025662 doses tested were many orders of magnitude higher than the planned clinical dose of PEG-60 kDa in Jivi (approximately 50,000-fold higher in the rat).	Based on these results, and according to the available literature, no acute toxicity is expected from the PEG molecule in Jivi.

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

Table SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Repeat dose toxicity	
Jivi	
In 2-week repeat-administration toxicity studies (dosing every other day for 14 days until neutralising antibodies develop) carried out in male and female rats [SN A48103 and SN PH-39043] and in male New Zealand White rabbits [SN T2079871], Jivi was administered at doses of 75, 750 or 2,250 IU/kg. The NOAEL was the highest dose tested, which represents 38 times the highest clinical dose of 60 IU/kg.	Results of the repeat-administration toxicity studies indicate a low order of toxicity for Jivi.
PEG-60 (BAY 1025662)	
BAY 1025662 was evaluated for systemic toxicity in a 4-week repeat-administration toxicity study [SN A50211 and SN PH-38066] in the male rat and rabbit. The effects of BAY 1025662 were assessed by clinical parameters, biochemistry, haematology and coagulation parameters, urinalysis, as well as determination of liver enzyme activity, full post-mortem examination and histopathology. The repeated intravenous administration (every other day) of BAY 1025662 over 4 weeks was well tolerated up to the highest dose tested in rats (11.0 mg/kg) and rabbits (2.0 mg/kg). Therefore, the NOAEL in these studies was the highest dose tested. According to the available literature (128-131), PEG molecules have been shown to be non-toxic, non-immunogenic and to reduce immunogenicity.	There are no safety concerns relating to the PEG-60 kDa molecule linked to rFVIII in Jivi, specifically no cellular vacuolation was seen histopathologically.
Chronic toxicology in Nude rats	
Chronic 26-week study with twice weekly intravenous dosing up to 1,200 IU/kg. There were no adverse clinical observations, body weight or food consumption changes or ophthalmology observations related to Jivi. No toxicologically important differences were noted in clinical pathology or urinalysis parameters. There were no Jivi-related macroscopic or microscopic findings or organ weight changes at weeks 13 and 26 in a full set of organs and tissues investigated. There was no indication of PEG accumulation in the brain or choroid plexus, kidney or spleen as demonstrated by the lack of a positive immunoreaction by immunohistochemistry examinations. The NOAEL was the highest dose of 1,200 IU/kg twice weekly.	The absence of visible accumulation of PEG by immunohistochemistry and the absence of any pathological findings makes the likelihood of developing clinical signs and symptoms related to PEG accumulation with chronic dosing in humans unlikely

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

Table SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Developmental and reproductive toxicity	
Jivi	
Males comprise the vast majority of PWHA, and clinical trials include male patients only. Clinical experience shows that there is no effect of recombinant factor VIII (rFVIII) on development, fertility and reproduction. In the single- and repeat-administration studies in male rats and rabbits, no treatment-related effects on the male reproductive organs were seen. Therefore, no developmental or reproductive toxicity studies were conducted in line with ICHS6R1. In the systemic toxicity studies (SN A48103 and SN T2079871), male reproductive organs were evaluated by histology to assess potential effects on these organs; no treatment-related effects were observed.	Based on the rare occurrence of haemophilia A in women, there is limited experience regarding the use of Kogenate FS/KOGENATE Bayer during pregnancy and breast-feeding. Therefore, Jivi should be used in pregnancy and lactation only if clearly indicated. FVIII does not cross the placenta and most likely will not be secreted into breast milk.
PEG-60 (BAY 1025662)	
In the PEG systemic toxicity study (SN A50211), male reproductive organs were evaluated by histology to assess potential effects on these organs including fertility; no treatment-related effects were observed. No adverse reproductive or teratogenic effects are reported with PEGs in the literature. PEGs are neither mutagenic nor carcinogenic (132, 133).	Based on the available literature, no reproductive toxicity is expected from PEG.
Nephrotoxicity Renal safety pharmacology parameters were included as part of the 2-week toxicity study of Jivi (SN A48103) in rats. No effects were seen up to the highest dose tested (2,250 IU/kg).	Non-clinical data do not give any indication of any risk of nephrotoxicity.
Hepatotoxicity In the systemic toxicity studies, no findings in liver were observed. Jivi is a PEGylated protein, and no active metabolites are expected.	Non-clinical data do not indicate any risk of hepatoxicity.

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

Table SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
Genotoxicity	
Jivi	
Because Jivi is a biological, genotoxicity studies are not relevant, and no genotoxicity studies were performed.	
PEG-60 (BAY 1025662)	
The maleimide linker structure was assessed by in-silico analysis. No structural alerts for genotoxicity were revealed.	The PEG 60 kDa-linker part in Jivi does not have a genotoxic potential.
A standard set of genotoxicity studies was conducted with the PEG-60-maleimide part (BAY 1025662) of Jivi. The Ames assay, the in vitro mouse lymphoma assay and the in vivo micronucleus study in rats (conducted as part of the 4-week repeat-administration toxicity study with BAY 1025662; {SN A50211} did not indicate any genotoxic potential of the PEG-60-maleimide-Cys up to the highest concentrations tested.	
Carcinogenicity	
Carcinogenicity studies are not considered relevant for this compound because FVIII is an endogenous human protein (ICH S6R1). PEG and FVIII products are not genotoxic and have been used in patients for many years without any indication of carcinogenic potential. Jivi is not expected to have any proliferative or immunomodulatory effects.	Based on experience of long-term use of Kogenate FS/Kogenate Bayer and of PEG, no carcinogenic potential is expected for Jivi.
General safety pharmacology Cardiovascular (including potential for QT interval prolongation) and respiratory systems Jivi is a similar protein with the same mechanism of action when compared with BAY 81-8973 (a full-length [FL]-rFVIII produced using a different manufacturing process in baby hamster kidney [BHK] 21 cells). BAY 81-8973 was tested in a cardiovascular safety pharmacology study after a short intravenous infusion to anaesthetized Beagle dogs without revealing significant effects.	The available data do not indicate any concern with regard to cardiovascular side effects.
Nervous system Effects of Jivi on central or peripheral nervous system function were studied in male rats after intravenous administration on Day 1 of the 2-week toxicity study. Jivi up to the highest dose tested did not show effects different from those of vehicle control.	The available data do not indicate any concern with regard to neurotoxicity.
Mechanisms for drug interactions	
Drug interaction studies are not applicable because Jivi is a coagulation protein. The pharmacological effects of	Pharmacodynamic interactions between Jivi and other drugs that may be used by

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

Table SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key safety findings (from non-clinical studies)	Relevance to human usage
drugs that may be used by PWHA act on distinct physiological systems. Therefore, pharmacodynamic interactions between them are not expected.	PWHA are not expected. Along with PEGylated drugs, PEG as such is widely used in medical practice. Its interaction with other pharmacological agents including biologicals is considered unlikely.
Other toxicity-related information or data <u>Juvenile animal studies</u> Juvenile animal studies in rats were conducted with Jivi (0, 200 and 1,000 IU/kg) and BAY 1025662 (0.4 and 2.0 mg/kg) administered twice per week for 4 weeks, with the first dose on postnatal day 17. This was requested by Health Canada. No toxicologically relevant test item-related effects were observed.	Results of the juvenile animal studies indicate a low order of toxicity for Jivi.
<u>*In vitro* human tissue cross-reactivity study</u> Jivi and BAY 14-2222 exhibited comparable binding to some endothelial cells of the heart and to very few endothelial cells in the kidney and lung. No binding was observed in human brain, liver, or spleen.	It can be concluded that the PEGylation of FVIII did not create any difference in tissue binding when compared with FL-FVIII without PEG.

IU: International Unit; kg: Kilogram; SN: Study Number; PEG: Polyethylene Glycol; PH: Pharma; mg: Milligram. PWHA: Patients with haemophilia A; QT: Time interval on the electrocardiogram.

No safety concerns were identified with this human recombinant protein in non-clinical studies. Therefore, there is no need for additional non-clinical data.

PART II: Module SIII - Clinical trial exposure

SIII.1 Brief overview of development

Jivi is a sterile, stable, purified, non-pyrogenic, dried protein concentrate of recombinant blood clotting rFVIII. It is a recombinant B-domain deleted (BDD) human coagulation FVIII variant that is site-specifically conjugated with a single 60 kDa branched polyethylene glycol (PEG) at an engineered cysteine replacing the amino acid in position 1,804. Jivi is produced using standard recombinant technology in baby hamster kidney cells (BHK21) into which the human FVIII gene has been introduced. BHK21 is the same host cell line used for the licensed full-length (FL)-rFVIII, Kogenate FS/Kogenate Bayer. Jivi is then purified with conventional chromatographic procedures. The purification process includes steps of viral clearance and clearance of host cell impurities before PEGylation. The purified FVIII undergoes a cysteine-specific PEGylation and subsequent purification with a cation exchange column. The formulation for Jivi contains a combination of standard excipients (NaCl, $CaCl_2$, histidine, glycine, sucrose, and Tween-80) with the same concentration as for the marketed FL-rFVIII, Kogenate FS/Kogenate Bayer.

Jivi, like FL-rFVIII (Kogenate FS/Kogenate Bayer or BAY 14-2222), is an inactive zymogen and after activation acts as a cofactor in the intrinsic coagulation pathway, but with an extended circulation half-life due to the PEG molecule.

Jivi is indicated for the treatment and prophylaxis of bleeding in PTPs aged ≥12 years of age with haemophilia A (congenital FVIII deficiency). It does not contain von Willebrand factor (vWF) and is not indicated in von Willebrand disease.

Marketing authorisation for Jivi has been granted. At the time of this RMP, four pivotal studies have been completed: (SNs 13401, 13024, 15912, 21824 [Part A]) including the extension parts of SN 13024 and SN 15912.

In addition, one phase 4 interventional study (SN 19764, PASS Category III) has been completed.

SIII.2 Clinical trial exposure

Definitions

Each day a patient is infused with FVIII is considered an exposure day (ED) independently of the number of infusions on that day. This is important since patient exposure to FVIII is inversely associated with the risk of inhibitor formation. According to their exposure, patients can be classified as previously untreated patients (PUPs) if they have never been exposed to exogenous FVIII before, or as PTPs if they have been multi-exposed to FVIII. A PTP is defined as a patient with >100 EDs (e.g., EMA pharmacovigilance guidance), or >150 EDs (International Society on Thrombosis and Haemostasis [ISTH] guidance). In clinical trials, patients with a low number of EDs (≤4 EDs) are termed minimally treated patients (MTPs).

In the phase 1 study 13401 as well as in the phase 2/3 study 13024, (PROTECT VIII) only patients who had been treated for a minimum of 150 EDs were enrolled (PTPs); in the phase 3

study 15912 (PROTECT Kids), children who had been treated for more than 50 EDs were enrolled; in the Phase 3 SN 21824 (Alfa-PROTECT), children who had been treated for minimum 50 EDs were enrolled.

In Phase 4 SN 19764 (PMI) patients who had been treated for a minimum of 150 EDs were enrolled.

Clinical trials

In the development of FVIII products in haemophilia there is no use of placebo. Therefore, the total exposure to Jivi in randomised, blinded trial populations is not presented in this report.

Completed/ongoing studies

Four pivotal clinical studies (study numbers 13401, 13024 15912, and 21824 [Part A]) have been completed including the extension parts of SN 13024 and SN 15912:

- Study 13401 was an open-label phase 1 trial aimed at evaluating the pharmacokinetics (PK) and safety profile of Jivi following single- and multiple-dose administration in 2 cohorts of male PTPs with severe haemophilia A. In total, 14 patients were treated for 8 weeks with Jivi at a low dose (25 IU/kg) twice weekly or a high dose (60 IU/kg) once weekly. For further details see **Annex 4**.
- Study 13024 was a phase 2/3, multicentre, partially randomised, open-label trial to investigate the safety and efficacy of on-demand and prophylactic treatment with Jivi in patients with severe haemophilia A (adolescents aged ≥12 years and adults) previously treated for ≥ 150 EDs. In part A of the study, patients were treated on-demand or prophylactically (by patient choice) with Jivi for 36 weeks. In the on-demand arm (n = 20), the dose of study drug was determined based on the location and severity of bleeding (maximum dose: 60 IU/kg). In the prophylaxis arm (n = 114 [4 of whom dropped out during the run-in period]), patients began treatment with 25 IU/kg twice weekly. After 10 weeks, patients with adequate bleed control (≤1 breakthrough bleed) were randomised 1:1 to 45 IU/kg every 5 days or 60 IU/kg every 7 days. Those with ≥2 breakthrough bleeds remained on twice weekly treatment at higher doses (30-40 IU/kg). Additional patients who were enrolled after the randomisation arms were filled, continued also in the 2x/week treatment arm. Patients could leave the treatment arm if bleeding control was considered inadequate. All patients completing the main study were offered participation in an optional extension phase. In part B of the study, patients requiring major surgical procedures received Jivi during their hospital stay and until discharge for up to three weeks (n = 14 patients [17 surgical procedures]; n = 3 patients [3 surgical procedures] in the extension). The appropriate dose and frequency of Jivi was determined based on PK measurements assessed prior to surgery. Part B is not included in the pool of data for the current exposure analysis because it relates to surgery (for further details see **Annex 4**).
- Study 15912 was a phase 3, multicentre, open-label clinical trial to evaluate the PK, safety and efficacy of Jivi in previously treated children (>50 EDs; <12 years of age).

This study did not begin until at least 20 patients in study 13024 had been evaluated for safety following at least 50 EDs (see also **Part II Module SIV.3**). The patients (n = 61) received at least 6 months (or the amount of time required to accumulate ≥50 EDs) of prophylactic treatment with Jivi in a regular schedule, with infusion at least once every 7 days. Subjects were treated with 25-60 IU/kg twice a week, 45-60 IU/kg every 5 days or 60 IU/kg every 7 days and were free to move between different regimes based on their bleed control. All patients completing the main study were offered participation in an optional extension phase (for further details see **Annex 4**). With Protocol Amendment 3 an expansion group (part 2; n = 12) was added to the study to evaluate further the safety of Jivi for the prophylaxis and treatment of bleeding in PTPs aged <6 years with haemophilia A. Treatment duration in this expansion group was 12 weeks, and the patients were then offered participation in an optional extension period. All patients were treated on a regular schedule (twice weekly) during the expansion study, and Jivi was also used for treatment of any breakthrough bleeding events. The pool of data for the current exposure analysis includes final data from the main part of the study, the expansion group (part 2), and the extension phase.

- SN 21824 is a Phase 3 multicentre, open-label clinical trial to evaluate the safety of Jivi infusions for prophylaxis and treatment of bleeding in previously treated children (>50 EDs) aged 7 to <12 years with severe haemophilia A. All patients completing the main study were offered participation in the extension phase (Part B). Part A has been completed; Part B is ongoing.

In addition, Phase 4 post-marketing interventional study (SN 19764, PASS Category III) has been completed. SN 19764 was a post-marketing investigation (PMI) open label Phase 4 study to assess safety and efficacy of Jivi (BAY 94-9027) treatment in patients with haemophilia A. This study consisted of prophylactic treatment with Jivi in pre-treated patients ≥ 18 years of age with severe haemophilia A. The study addressed regulatory requirements to assess safety in 200 participants treated with 100 EDs, including participants from the clinical development program in studies 13024 PROTECT VIII (Phase 2/3) and 15912 PROTECT Kids (Phase 3). Total of 32 patients were included in the PMI study.

The pool of data for the exposure analysis includes final data of the above-mentioned studies.

Part II: Module SIII - Clinical trial exposure

Table SIII-1: Overview of the clinical development programme for Jivi

Study number (Phase)	Design	Study objectives	Jivi dose and treatment duration	Study population; age	Study size (N)
13401 (phase 1)	Open-label	To evaluate the PK and safety profile of Jivi following single- and multiple-dose administration	Group 1: Single dose of Kogenate FS 25 IU/kg followed by Jivi 25 IU/kg given 2x/week for 8 weeks	Male PTPs; 21-58 years (mean: 36 years)	7
			Group 2: Single dose of Kogenate FS 50 IU/kg followed by Jivi 60 IU/kg given 1x/week for 8 weeks		7
13024 (phase 2/3)	Multicentre, partially randomised, open-label	To investigate safety and efficacy of on-demand and prophylactic treatment with Jivi	Part A – Arm 1 (on-demand): Jivi as needed for 36 weeks	Male PTPs; 12-65 years	20
			Part A – Arm 2 (prophylaxis for 36 weeks)		
			• Run-in (10 weeks): Jivi 25 IU/kg 2x/week		114 (All patients in Arm 2)[a]
			• ≥2 breakthrough bleeds during run-in		
			• Group 1: Jivi 30–40 IU/kg 2x/week		13
			• ≤1 breakthrough bleed during run-in		
			• Randomised – Group 2: Jivi 45-60 IU/kg every 5 days		43
			• Randomised – Group 3: Jivi 60 IU/kg 1x/week		43
			• Not randomised (due to cap on numbers) – Group 4: Jivi 30–40 IU/kg 2x/week		11

Part II: Module SIII - Clinical trial exposure

Table SIII-1: Overview of the clinical development programme for Jivi

Study number (Phase)	Design	Study objectives	Jivi dose and treatment duration	Study population; age	Study size (N)
			Part B – Major surgery:[b] Jivi as needed (during hospital stay and until discharge for up to 3 weeks); loading dose of 50 IU/kg ≤60 min prior to procedure; 15-50 IU/kg repeated as indicated		16[c] (Optional arm)
13024 (phase 2/3) extension[c]	Optional, open-label extension of study 13024	To assess long-term safety of Jivi over ≥100 accumulated EDs (main study plus extension)	Study 13024 part A extension (see above)[d]	See above	121
			Study 13024 part B extension (see above)[b]		19[d]
15912 (phase 3)	Multicentre, open-label	To evaluate PK, safety and efficacy of Jivi	Part 1 – prophylaxis for ≥6 months (or ≥50 EDs) Infusion of 25–60 IU/kg twice a week, 45–60 IU/kg every 5 days and 60 IU/kg every 7 days.	PTPs; < 12 years	61
			Part 2 (expansion group) – prophylaxis for 12 weeks Infusion 2x/week 25–60 IU/kg	PTPs; < 6 years	12
15912 (phase 3) extension[c]	Optional, open-label extension of study 15912	To assess long-term safety of Jivi over ≥50 additional EDs	Study 15912 extension (see above)	See above	59
21824 (Phase 3)	Multicentre, open-label	To investigate safety of Jivi for prophylaxis and treatment of bleeding	Part A – prophylaxis for ≥6 months (or ≥50 EDs) Infusion of 40–60 IU/kg twice a week	PTPs; 7 to <12 years	35

Part II: Module SIII - Clinical trial exposure

Table SIII-1: Overview of the clinical development programme for Jivi

Study number (Phase)	Design	Study objectives	Jivi dose and treatment duration	Study population; age	Study size (N)

[a] Four patients dropped out during the run-in period, leaving 110 patients to be assigned to groups 1–4 at week 10.
[b] Not included in the pool of data for the exposure analysis presented in this Module.
[c] The safety population consisted of 14 patients who underwent surgery and 2 additional patients included for PK analysis who did not undergo surgery.
[d] Three additional patients (with 3 surgical procedures) included in the extension study.
[e]52 patients from the Main study and 7 patients from part 2 participated in the extension.
ED: Exposure Day; IU: International Unit; PK: Pharmacokinetics; PTP: previously treated patient; SN: Study Number; ≥: Greater than or equal to; <: Less than.

The exposure data from the pooled analysis of Jivi SNs 13401, 13024 part A including extension part (excluding subjects enrolled for Part B only), SN 15912 (main part and part 2) and extension, SN 21824 (Part A) and from the Phase 4 SN 19764 is included in this RMP.

Table SIII-2: Study sample sizes by study number (safety analysis set)

Study Number	SN 13024	SN 13401	SN 15912	SN 21824	SN 19764	Total
<7 years	0	0	48	0	0	**48**
≥7 years	134	14	25	35	32	**240**
Total	**134**	**14**	**73**	**35**	**32**	**288**

Number of subjects enrolled are the number of subjects who signed informed consent.
13024: part A including extension part (excluding subjects enrolled for Part B only)
13401: The initial Kogenate FS single dose PK period is excluded.
15912 (main part and part 2) and extension
21824 (Part A)
19764
≥: Greater than or equal to; <: Less than; SN: Study Number.

Table SIII-3: By age group

Treatment and prophylaxis of bleeding in PWHA		
Age group	**Persons**	**Person time (years)**
0 to <2 years	0	0
2 to <6 years	44	154.2
6 to <12 years	64	171.6
12 to <18 years	13	48.9
18 to 65 years	164	446.6
> 65 years	3	4.3
Total	**288**	**825.6**

Person time is given in years (1 year is 360 days).
Data are shown from studies (SNs. 13401, 13024 Part A including extension part (excluding subjects enrolled for Part B only), 15912 (main part and part 2) and extension, 21824 (Part A), 19764)
PWHA: Patients with Haemophilia A; SN: Study Number; <: Less than; >: Greater than

Table SIII-4: Duration of exposure in age groups (<7 years/≥7 years) and overall

Treatment and prophylaxis of bleeding in PWHA			
Age group at enrolment	**Duration of exposure (person time)**	**Persons**	**Person time (years)**
<7 years	at least 1 month	47	173.5
	at least 3 months	41	172.6
	at least 6 months	39	172.0
	at least 12 months	35	169.1
	at least 24 months	32	164.1
	Total duration of exposure	48	173.6
≥7 years	at least 1 month	235	651.8
	at least 3 months	219	648.9
	at least 6 months	199	640.1
	at least 12 months	169	621.5
	at least 24 months	112	536.6
	Total duration of exposure	240	652.0
Total	at least 1 month	282	825.3
	at least 3 months	260	821.4
	at least 6 months	238	812.0
	at least 12 months	204	790.6
	at least 24 months	144	700.7
	Total duration of exposure	288	825.6

Data are shown from studies (SNs. 13401, 13024- Part A including extension part (excluding subjects enrolled for Part B only), 15912 (main part and part 2) and extension, 21824 (Part A), 19764
Person time is given in years (1 year is 360 days, 1 month is 30 days)
PWHA: Patients with Haemophilia A; SN: Study Number; <: Less than; ≥: Greater than or equal to

Table SIII-5: By minimum number of exposure days at baseline in age groups (<7 years / ≥7 years) and overall

Treatment and prophylaxis of bleeding in PWHA			
Age group at enrolment	**Minimum number of exposure days at baseline**	**Persons[a]**	**Person time[b] (years)**
<7 years	PTP, at least 50 ED according to protocol	48	173.6
	PTP, at least 150 ED according to protocol	0	
≥7 years	PTP, at least 50 ED according to protocol	60	152.2
	PTP, at least 150 ED according to protocol	180	499.8
Total	PTP, at least 50 ED according to protocol	108	325.8
	PTP, at least 150 ED according to protocol	180	499.8

[a] Patients are categorized according to the inclusion criteria of the studies (SNs. 13024, 13401 and 19764: at least 150 ED; SN 15912, 21824: at least 50 ED). The actual number of EDs at baseline might be higher.
[b] Person time is given in years (1 year is 360 days).
Data are shown from studies (SNs. 13401, 13024- Part A including extension part (excluding subjects enrolled for Part B only), 15912 (main part and part 2) and extension, 21824 (Part A), 19764)
ED: Exposure Day; PWHA: Patients with Haemophilia A; SN: Study Number; PTP: Previously Treated Patient; <: Less than; ≥: Greater than or equal to.

Table SIII-6: By dose in age groups (<7 years and ≥7 years) and overall

Age group at enrolment	**Dose**	**Persons**	**Person time (years)**
<7 years	On-demand	0	
	Regular prophylaxis	48	173.6
	Twice a week	17	37.0
	Every 5 days	12	43.4
	Every 7 days	5	21.9
	Other	14	71.4
	On-demand/regular prophylaxis	0	
	Total	**48**	**173.6**
≥7 years	On-demand	17	48.2
	Regular prophylaxis	220	596.3
	Twice a week	87	131.0
	Every 5 days	47	159.0
	Every 7 days	35	82.2
	Other	51	224.1
	On-demand/regular prophylaxis	3	7.5
	Total	**240**	**652.0**
Total	On-demand	17	48.2
	Regular prophylaxis	268	769.9

Table SIII-6: By dose in age groups (<7 years and ≥7 years) and overall

Age group at enrolment	Dose	Persons	Person time (years)
	Twice a week	104	167.9
	Every 5 days	59	202.4
	Every 7 days	40	104.0
	Other	65	295.5
	On-demand/regular prophylaxis	3	7.5
	Total	**288**	**825.6**

Person time is given in years (1 year is 360 days).
'Other' includes subjects that switched between prophylaxis regimens. 'On-demand/regular prophylaxis includes subjects that switched from on-demand to regular prophylaxis.
Data are shown from studies (SNs. 13401, 13024- Part A including extension part (excluding subjects enrolled for Part B only), 15912 (main part and part 2) and extension, 21824 (Part A), 19764)
13024: The initial run-in period of 10 weeks is not considered for identification of dosing frequency.
<: Less than; ≥: Greater than or equal to.

Table SIII-7: By ethnic or racial origin in age groups (<7 years/≥7 years) and overall

Treatment and prophylaxis of bleeding in PWHA			
Age group at enrolment	**Racial origin**	**Persons**	**Person time (years)**
<7 years	White	40	143.3
	Black or African American	3	11.2
	Asian	3	9.2
	American Indian/Alaska Native	1	6.4
	Native Hawaiian/Pacific Islander	1	3.4
	Not reported	0	0
≥7 years	White	190	544.6
	Black or African American	6	13.3
	Asian	33	67.6
	American Indian/Alaska Native	0	
	Native Hawaiian/Pacific Islander	0	
	Not reported	11	26.5
Total	White	230	687.9
	Black or African American	9	24.5
	Asian	36	76.9
	American Indian/Alaska Native	1	6.4
	Native Hawaiian/Pacific Islander	1	3.4
	Not reported	11	26.5

Person time is given in years (1 year is 360 days).

Part II: Module SIII - Clinical trial exposure

Table SIII-7: By ethnic or racial origin in age groups (<7 years/≥7 years) and overall

Treatment and prophylaxis of bleeding in PWHA			
Age group at enrolment	**Racial origin**	**Persons**	**Person time (years)**

Data are shown from studies (13401, 13024- Part A including extension part (excluding subjects enrolled for Part B only), 15912 (main part and part 2) and extension, 21824 (Part A), 19764)
PWHA: Patients with Haemophilia A; SN: Study Number; <: Less than; ≥: Greater than or equal to

Table SIII-8: Special populations in age groups (<7 years/≥7 years) and overall

Treatment and prophylaxis of bleeding of bleeding in PWHA			
Age group at enrolment	**Special populations**	**Persons**	**Person time**
<7 years	Renal impairment	1	5.8
≥7 years	Renal impairment	2	13.5
	Hepatic impairment total	113	327.7
	Hepatitis	110	320.3
	HIV	23	60.6
Total	Renal impairment	3	19.4
	Hepatic impairment total	113	327.7
	Hepatitis	110	320.3
	HIV	23	60.6

Person time is given in years (1 year is 360 days).
Data are shown from studies (SNs. 13401, 13024- Part A including extension part (excluding subjects enrolled for Part B only), 15912 (main part and part 2) and extension, 21824 (Part A), 19764)
Renal impairment: Subjects with medical history of renal impairment defined *via* High Level Group Term (HLGT) “Renal disorders (excl nephropathies)” and HLGT “Nephropathies”.
Hepatic impairment total: Subjects with medical history of hepatic impairment defined *via* HLGT “Hepatic and hepatobiliary disorders”, including High Level Term (HLT) “Hepatic viral infections”.
Hepatitis: Subjects with medical history of hepatitis defined *via* HLT “Hepatitis viral infections”.
Human immunodeficiency virus (HIV): Subjects with medical history of HIV defined *via* HLT “Acquired immune deficiency syndromes”, HLT “Retroviral infections”, Preferred 13.5rm (PT) “HIV antibody positive”, and PT “HIV test positive”.
PWHA: Patients with Haemophilia A; SN: Study Number; <: Less than; ≥: Greater than or equal to.

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

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

Table SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing information Yes (Y)/No (N)	Rationale
1. Known hypersensitivity to the drug substance, any of its components, or hamster protein	Known hypersensitivity to the drug substance or any of its components (including hamster or mouse protein) is listed as a contraindication in the Summary of Product Characteristics (SmPC)	N	Will remain a contraindication
2. Non-severe haemophilia A (≥1% FVIII)	Only patients with severe haemophilia A (<1% FVIII) are included, as this patient group requires more frequent treatment with FVIII than patients with non-severe haemophilia. Prophylaxis treatment is mainly used for severe haemophilia A. This also ensures homogeneity of the study populations, appropriate assessment of immunogenicity and timely completion of the studies.	N	Patients with mild and moderate haemophilia A were included in post-marketing observational studies of Kogenate Bayer, Jivi, and Kovaltry No significant conspicuous findings different from those observed in patients with severe haemophilia A became obvious. Patients with mild or moderate haemophilia also do not require prophylaxis therapy, just occasional treatment for bleeds or prophylaxis for surgeries.
3. Adults aged >65 years	Patients with haemophilia in this age group are rare and often are unwilling to receive frequent prophylactic injections. For participation in	Y	Patients were excluded from pivotal studies, so population is not adequately characterised. In high-risk patients >65 years

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

Table SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing information Yes (Y)/No (N)	Rationale
	clinical trials, patients must be able to enter infusion data in electronic diaries. This may be challenging for the patients aged >65 years.		of age, substitution therapy with FVIII may add to cardiovascular risk (**see Part II Module SVII.1.2**).
4. Previously treated patients (PTPs) without a high level of exposure to FVIII (≤50 or <150 exposure days (EDs) in patients aged <12 years or 12-65 years, respectively)	Patients with a high level of exposure should be immunotolerant to FVIII and are therefore considered a suitable population for the evaluation of *de novo,* product-specific inhibitor formation.	N	The proposed indication for Jivi in patients ≥7 years of age will exclude such patients.
5. Female patients	Due to the recessive nature of this X-linked disease, women are affected only rarely and therefore are not included in the clinical trials.	N	Clinical experience with Kogenate Bayer and Kovaltry, and other FVIII products, has not identified differences between sexes.
6. Abnormal renal function (serum creatinine >1.5 × or >2 × the upper limit of the normal range [ULN] in study 13401 or studies 13024, 15912, and 21824, respectively)	To reduce the impact of co-morbidities on the homogeneity of the study population (kidney disease is associated with abnormal haemostasis) (134).	Y	Patients were excluded from pivotal studies, so population is not adequately characterised. The polyethylene glycol (PEG) moiety of Jivi is expected to be secreted in urine. The only PEG-related finding reported in the literature and observed in some animal studies at extremely high PEG doses after repeated administration, was vacuolation of certain cell types, including renal tubule cells. No vacuolation was observed in non-

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

Table SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing information Yes (Y)/No (N)	Rationale
			clinical studies with Jivi. The probability, nature and functional consequences of such findings are not completely understood. PEG doses with Jivi are very low. (**see Part II Module SVII.1.2**)
7. Active hepatic disease (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] levels >2 × or >5 × the ULN [in study 13401 or studies 13024 and 15912, respectively])	To reduce the impact of co-morbidities on the homogeneity of the study population (liver disease is associated with abnormal haemostasis) (135).	Y	Patients were excluded from pivotal studies, so population is not adequately characterised. The PEG moiety of Jivi is expected to be secreted in urine, and to a lesser extent, in bile. The only PEG-related finding reported in the literature and observed in some animal studies at extremely high PEG doses after repeated administration, was vacuolation of certain cell types, including liver cells. No vacuolation was observed in non-clinical studies with Jivi. The probability, nature and functional consequences of such findings are not completely understood. PEG doses with Jivi are very low (**see Part II Module SVII.1.2**).

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

Table SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing information Yes (Y)/No (N)	Rationale
8. Any inherited or acquired bleeding disorder in addition to haemophilia A	Patients with additional bleeding disorders are excluded from the clinical trial programme to ensure homogeneity of the study populations.	N	FVIII is indicated for treatment of haemophilia A. Other bleeding disorders require different factors to generate coagulation.
9. Documented history or current evidence of inhibitor to FVIII with a titre ≥0.6 Bethesda Units (BU), or clinical history suggestive of inhibitor requiring modification of treatment	Only patients without evidence of inhibitors are included, to enable detection of *de novo* inhibitor formation.	N	The formation of neutralising antibodies (inhibitors) to FVIII is a known complication in the management of individuals with haemophilia A. Development of FVIII inhibitors is an important identified risk (**see Part II Module SVII.1.2**).
10. Requirement for chemotherapy, chronic oral or intravenous corticosteroid use, or treatment with immunomodulatory drugs other than anti-retroviral chemotherapy within the last 3 months prior to study entry or during the study (brief courses of prednisone/methylprednisone [<14 days] are permitted)	Patients should not receive treatment with immunomodulatory or immunosuppressive agents, in order to determine the immunogenicity of the new drug in immunocompetent patients.	N	No drug–drug interaction is expected, and no immunosuppressant activity is likely. See above
11. Platelet count <100,000/mm^3	To ensure homogeneity of the study population and to exclude other causes of bleeding events.	N	FVIII is pro-coagulant, and no interaction is expected.
12. Current participation in another investigational drug study or participation in a clinical study involving an investigational drug within 30 days of study entry (studies	To protect patients and exclude carry-over effects from other investigational drugs	N	This is a standard clinical trial exclusion criterion.

Table SIV-1: Exclusion criteria in the pivotal studies across the development program which are proposed/not proposed to be considered as missing information

Exclusion criteria	Reason for exclusion	Missing information Yes (Y)/No (N)	Rationale
with marketed FVIII are allowed)			

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BU: Bethesda Units; CCDS: Company Core Data Sheet; ED: Exposure Day; PEG: Polyethylene Glycol; N/No: Number; mm^3: Millimetre cube; ULN: Upper Limit of The Normal Range; SN: Study Number; <: Less than; >: More than; ≥: Greater than or equal to.

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

The clinical development programme is unlikely to detect certain types of ARs such as those that are rare or with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically underrepresented in clinical trial development programmes

Table SIV-2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Children	The paediatric population was included in three clinical trials of Jivi. In the Phase 2/3 SN 13024, previously treated male patients of age ≥12 years with severe haemophilia A have been enrolled. Efficacy during long-term treatment in the extension study could be demonstrated for treatment durations of up to seven years. In the Phase 3 SN 15912, children aged <12 years who have already received a FVIII product for at least 50 EDs have been enrolled in two cohorts, 6≤12 years and <6 years of age. The first cohort started after at least 20 patients in SN 13024 had been evaluated for safety following at least 50 EDs. In the Phase 3 SN 21824, previously treated male patients of age 7 to <12 years with severe haemophilia A have been enrolled. Safety could be demonstrated for treatment duration of up to six months in the completed Part A of the study. Use of Jivi is limited to patients ≥7 years in the proposed label.

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

Table SIV-2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Elderly	Patients older than 65 years were not included in the pivotal studies for Jivi. A small number of patients >65 years of age (3 patients in total, 66-68 years of age) were included in the Phase 4 Study (SN 19764). In addition, a subgroup of patients in study 13024 reached the age of ≥65 years during the extension study (maximum 67 years). Clinical experience with anti-haemophilia factor has not identified differences between the elderly and younger patients. In general, co-morbidities associated with aging are also challenges in the haemophilia population. Patients with haemophilia might have risk factors for cardiovascular diseases, even though they might be protected against thrombus formation to a certain degree. This is summarized in the CCDS section 4.4.4.
Pregnant or breast-feeding women	Women are not included in the clinical development program of Jivi. In non-clinical studies, Jivi has only been studied in male animals. Congenital haemophilia A is an X-linked recessive disorder affecting almost exclusively males. Women are carriers for this disease, and haemophilia A occurs only rarely in women. According to the post-marketing experience with recombinant anti-haemophilia factors, it is not known whether rFVIII can cause foetal harm. In humans no polyethylene glycol (PEG)-related toxicities have been reported for PEGylated therapeutic proteins, but data on pregnancy and lactation are unavailable for Jivi. Therefore, Jivi should not be used during pregnancy and lactation unless the benefits clearly outweigh any potential risk.
Patients with relevant comorbidities:	
• Patients with hepatic impairment	Patients with liver disorders such as hepatitis (mainly HCV-related) were included in the Phase 2/3 and Phase 3 clinical trials of Jivi. However, patients with active liver disease (defined as aspartate aminotransferase or alanine aminotransferase levels more than five times the upper limit of normal) were excluded, and data for these patients are therefore not available.
• Patients with renal impairment	Patients with abnormal renal function (serum creatinine >1.5 × or >2 × the ULN in SN 13401 or SNs 13024,15912, and 21824, respectively) are not investigated in clinical trials of Jivi.
• Patients with other relevant co-morbidity	Patients with previous inhibitor formation are not included in the clinical development program of Jivi. The main reason is to assess the risk of *de novo* inhibitor formation. Most frequent co-morbidities are related to the haemophilic arthropathies which are present in most adult haemophilia patients. Also, HIV was a relevant co-morbidity in 8% of the clinical trial population.

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

Table SIV-2: Exposure of special populations included or not in clinical trial development programs

Type of special population	Exposure
Patients with a disease severity different from the inclusion criteria in the clinical trial population	Patients with mild and moderate haemophilia A are excluded from clinical trials of Jivi. Reasons to include only patients with severe haemophilia A were: (i) the fact that patients with severe haemophilia have virtually no circulating FVIII; this allows for a greater accuracy of the pharmacokinetic evaluation of FVIII levels, reducing the variability inherent in these types of studies; (ii) the increased bleeding frequency in patients with severe haemophilia, which ensures a sufficient number of EDs to the study drug in a relatively short period and the need for prophylaxis treatment in order to adequately evaluate both efficacy and safety; (iii) the fact that patients with severe haemophilia are at higher risk of FVIII inhibitor development than patients with mild and moderate disease, and are thus more suitable for prospective assessment of immunogenicity. Patients with mild and moderate haemophilia A were included in post-marketing observational studies with Jivi and Kogenate FS/Kogenate Bayer and Kovaltry. No significant findings different from those observed in patients with severe haemophilia A were seen. According to recent literature (136, 137), there seems to be an increased risk of development of inhibitors in patients with mild and moderate haemophilia A during intensive treatment with rFVIII as part of the perioperative management or for a bleeding episode. Since patients with mild to moderate haemophilia rarely receive prophylactic treatment, the development of inhibitors in these patients is an infrequent complication but is increasingly recognized in the surgical setting.
Sub-populations carrying known and relevant polymorphisms	NA
Patients of different racial and/or ethnic origin	No patients are excluded from clinical trials with Jivi due to their racial or ethnic origin. Race is a risk factor for inhibitor development in patients with severe haemophilia A. This risk appears to be higher in black and Hispanic patients possibly due to socioeconomic and genetic factors. However, this phenomenon is still not fully understood (138). Of the 288 patients included in SN 13401, 13024 part A, 15912 main part and expansion (part 2), 21824 and 19764 230 (79.8%), were white, 36 (12.5% were Asian, nine (3.1% were black or African American, one was an American Indian or Alaska Native, and one was a Native Hawaiian or other Pacific Islander (race was not reported for the remaining 11[3.8%] patients). Thirty patients (10.4%) were of Hispanic or Latino ethnicity.

CCDS: Company Core Data Sheet; ED: Exposure Day; No.: Number; NA: Not Applicable; SN: Study Number
PEG: Polyethylene Glycol, HCV: Hepatitis C Virus; ULN: Upper Limit of The Normal Range; %: Percent.

PART II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

The first marketing authorization for Jivi was granted in the US on 29 AUG 2018 and the first launch was on 04 SEP 2018 in the US followed by the approval in Canada (OCT 2018) and the EU (NOV 2018). At the DLP of this RMP, Jivi is currently authorized to be marketed in 53 countries and marketed in 31 countries.

SV.1.1 Method used to calculate exposure

The method used to calculate exposure assumes that the average amount of product used in the post-marketing is the same as the amount used during the clinical trials where the dose could be adjusted by the investigator according to the patient's needs. The total number of patient years of exposure was calculated by taking the total number of IUs of Jivi sold divided by the average annual dose per patient in the PROTECT VIII clinical trial for prophylaxis use in patients ≥12 years of age. This average dose is 271,344 IU/year/patient.

SV.1.2 Exposure

As of the most recent periodic safety update report (DLP 28 AUG 2023), 299 patients had been exposed to Jivi in completed clinical trials and 49 patients were estimated to have been exposed to Jivi in ongoing clinical trials.

The non-clinical trial exposure since marketing authorisation to 31 MAR 2024 is estimated at 5,438 patient-years.

The distribution by region is provided in Table SV-1.

Table SV-1: Jivi world-wide patient exposure in patient years

Region	Cumulative exposure (Patient-Years)
EU	2,748
US	1,516
Asia	605
Rest of world	569
Total	5,438

EU: European Union; US: United States

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

SVI.1 Potential for misuse for illegal purposes

Based on the post-marketing experience with Jivi, there is no evidence of misuse for illegal purposes.

PART II: Module SVII - Identified and potential risks

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

Additional details of the changes to the EU RMP overtime are provided in **Annex 8**.

The frequency of AEs defined as important identified or potential risks from clinical trials of Jivi are presented in this section. The side effects and important identified risks of Jivi are similar to those experienced with other FVIII products.

In the following, important identified risks are defined as those that are likely to have an impact on the risk–benefit balance of the product. An important identified risk to be included in the RMP would usually warrant further evaluation as part of the pharmacovigilance plan (e.g., to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use, which populations are particularly at risk); risk minimisation activities: product information advising on specific clinical actions to be taken to minimise the risk. The important potential risks to be included in the RMP are those important potential risks that, when further characterised and if confirmed, would have an impact on the benefit- risk balance of the product. Missing information relevant to the risk management planning refers to gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation (e.g., long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterised so far.

Adverse event frequencies have been assessed using data from 3 clinical studies (study numbers 13401, PROTECT FVIII, 13024, and 15912, PROTECT Kids), which are complete.

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

All below risks were considered to be risks with minimal clinical impact on patients (in relation to the severity of the indication treated, or ARs with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated).

Table SVII-1: Risks not considered important for inclusion in the lost of safety concerns

Medical Dictionary for Regulatory Activities (MedDRA) Standard	Frequency Overall N (%)	Frequency in Patients ≥12 Years of Age N (%)
Gastrointestinal disorders		
Abdominal pain	9 (4.1%)	5 (3.4%)
Nausea	9 (4.1%)	8 (5.4%)
Vomiting	10 (4.5%)	5 (3.4%)
General Disorders and Administration Site Conditions		
Injection site reactions[A]	4 (1.8%)	2 (1.4%)
Pyrexia	20 (9.0%)	8 (5.4%)
Nervous System Disorders		
Dizziness	3 (1.4%)	3 (2.0%)
Dysgeusia	1 (0.5%)	0
Headache	29 (13.1%)	21 (14.2%)
Psychiatric disorders		
Insomnia	5 (2.3%)	4 (2.7%)
Respiratory, thoracic and mediastinal disorders		
Cough	18 (8.1%)	10 (6.8%)
Skin and subcutaneous tissue disorders		
Erythema[B]	3 (1.4%)	2 (1.4%)
Pruritus	2 (0.9%)	1 (0.7%)
Rash[C]	9 (4.1%)	3 (2.0%)
Vascular disorders		
Flushing	1 (0.5%)	1 (0.7%)

[A] includes Injection site pruritus and Injection site rash.
[B] includes Erythema and Erythema multiforme.
[C] includes Rash and Rash papular.
%: Percent; ≥: Greater than or equal to; MedDRA: Medical Dictionary for Regulatory Activities; N: Number

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

Table SVII-2: Overview of important identified risks

Important identified risks	Scientific evidence and Risk–Benefit Impact
Development of FVIII inhibitors	The development of antibodies to factor VIII (FVIII) with neutralising properties (known as FVIII inhibitors) may have a great impact on treatment of patients with haemophilia. Therefore, inhibitor development is considered a medically significant event, and it is regarded as the most serious complication of FVIII replacement in

	patients with haemophilia.
Hypersensitivity reactions	Hypersensitivity reactions have been observed in the clinical trial program only during the 1st 4 exposure days (EDs). These events were usually mild to moderate in intensity and resolved rapidly upon discontinuation of drug administration. Hypersensitivity may also be related to an immune response to polyethylene glycol (PEG). In patients ≥12 years the incidence of hypersensitivity reactions associated with anti-PEG antibodies was 0.7% (95% confidence interval [CI] 0-2.0%).
Loss of efficacy associated with anti-PEG antibodies	Loss of efficacy associated with development of anti-PEG antibodies has been identified in clinical trials following administration of the 2nd to 4th dose. In cases of loss of efficacy due to anti-PEG antibodies, it may be necessary to discontinue treatment with Jivi, and switch to another therapeutic option such as the previous FVIII treatment.

%: Percent; ≥: Greater than or equal to; CI: Confidence Interval; ED: Exposure Day; FVIII: factor VIII; PEG: Polyethylene Glycol

Table SVII-3: Overview of important potential risks

Important potential risks	Scientific evidence and Risk–Benefit Impact
Off-label use	
Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs	The risk of clinical effects related to PEG accumulation in organs with chronic use of Jivi is very low for the following reasons. • The non-clinical long-term 6-months toxicology study[a] of Jivi demonstrated no visible accumulation of PEG in the brain including choroid plexus, kidney or spleen as demonstrated by the lack of a positive immunoreaction to anti-PEG monoclonal antibodies (mAb) by immunohistochemistry examinations. • Excretion of PEG via urine has been demonstrated in non-clinical studies reported in literature. Steady state for PEG distribution in all organs is expected after 3-4 years. • Clinical studies of Jivi demonstrated that the plasma PEG concentration of Jivi at steady state is low (at or below 0.1 mg/L). Although the scientific evidence available shows that this risk is very small, there is a possibility that long-term accumulation of PEG could have a clinical effect.
Thromboembolic Events	Thromboembolic events have not been reported with Jivi which is in contrast to other agents such as Hemlibra. Normalization of FVIII levels in patients with existing cardiovascular risk factors have the potential to result in thromboembolic events.

Table SVII-4: Overview of missing information

Missing information	Scientific evidence and Risk–Benefit Impact
Use in patients with severe hepatic impairment	Patients were excluded from pivotal studies, so this population is not adequately characterised. The polyethylene glycol (PEG) moiety of Jivi is expected to be secreted in urine, and to a lesser extent, in bile. At extremely high PEG doses after repeated administration, vacuolation of Kupffer cells and hepatocytes have been reported with other PEGylated products. Based on the findings from the chronic toxicology study with Jivi, clinically relevant accumulation of PEG in the liver in patients with severe hepatic impairment is not expected. During the clinical extension studies, no change in hepatic function was observed in patients with mild to moderate hepatobiliary disorders (mainly hepatitis C virus [HCV]).
Use in patients with renal insufficiency	Patients were excluded from pivotal studies, so population is not adequately characterised. The PEG moiety of Jivi is expected to be secreted primarily in urine. Therefore, plasma PEG levels will increase with worsening renal insufficiency. The amount of PEG in each dose of Jivi is very low. Modelling shows that 90% loss of renal clearance results in plasma PEG concentration of not more than 1.0 mg/L which is below PEG concentrations measured in patients with normal renal function using approved pegylated medicinal products[b].
Use in elderly patients >65 years of age	Patients were excluded from pivotal studies, so population is not adequately characterised. In high-risk patients >65 years of age with existing cardiovascular risk factors, substitution therapy with FVIII may increase cardiovascular risk. There is limited experience in patients >65 years.
Safety profile in women including pregnancy and lactation	There is limited data on women with haemophilia on Jivi

[a] Submitted with Day 120 response to question 135
[b] Submitted in day 120 response to question 194 and Module 4.2.2.7 PH-39907, Section 1 Summary
>: Greater Than; HCV: Hepatitis C Virus; L: Litre; mg: Milligram; PEG: Polyethylene Glycol;

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

This risk management plan is submitted to support the extension of the indication to include PTP patients with Haemophilia A age ≥7 years (Type II C.I.6 [Extension of indication] Procedure EMEA/H/C/004054/II/0034).

No new safety concerns were identified since the submission of the previous approved RMP, version 2.1.

The safety concerns included in the previous RMP (version 2.1) were updated with relevant information to include data from the Alfa-PROTECT study (SN 21824, part A), the completed Phase 4 PMI study (SN 19764), and up-to-date post-marketing experience and are maintained in the RMP.

Section SVII.3 was amended to list the important potential risks "Thromboembolic events", "Off-label use" and "Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs" for consistency of presentation (previously included only in section SVII.1), which are retained in the EU RMP.

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

SVII.3.1.1 Important identified risk: Development of FVIII inhibitors

Frequency with 95% CI

Clinical trials (all clinical trial populations including open extension):

At the time of this RMP, four pivotal studies, including one phase 1 study (SN 13401), three phase 3 studies (PROTECT FVIII [SN 13024], PROTECT Kids [SN 15912], and Alfa-PROTECT [SN 21824] (Part A)), and one interventional phase 4 study (SN 19764)) have been completed including the extension parts of SNs 13024 and 15912. No confirmed case of new inhibitor development was reported in these studies with Jivi in PTPs.

Fourteen PTPs were enrolled in study no. 13401. No inhibitor development was reported (no individual had a positive FVIII inhibitor level [≥0.6 Bethesda Unit {BU}/mL; Nijmegen modified Bethesda assay]).

In Part A of study 13024 (n = 134), no FVIII inhibitor antibodies were seen in patients receiving 36 weeks of treatment with Jivi. During the extension period (N = 121), one subject in Part A had a transient low-titre FVIII inhibitor result of 1.4 BU/mL which was not confirmed in the second sample that was negative.

In Part B (which included 14 patients who underwent major surgery), there were 2 reports of positive low-titre inhibitors: 1 involved a patient who had a positive inhibitor test pre-surgery which was not confirmed by repeat testing (this positive test was after one infusion of study drug for pharmacokinetic [PK] evaluation), and the other involved a patient who already had a low-titre FVIII inhibitor (0.5 BU) during screening (this patient had no prior exposure to Jivi).

Study 15912 included 61 PTPs aged <12 years in the main part and 12 PTPs aged <6 years in part 2. No FVIII inhibitor antibodies were detected in this paediatric study. During the extension part of SN 15912 three subjects had transiently detectable positive (≥0.6 BU/mL) FVIII inhibitor levels, only at single instances. None of the inhibitors were confirmed, as all follow-up tests were negative.

In Part A of SN 21824 (n = 35) no FVIII inhibitor antibodies were seen in patients receiving 50 EDs (6 months) of treatment with Jivi.

During the Phase 4 PMI study (SN 19764) there were no participants with a positive FVIII inhibitor measurement amongst 32 treated participants.

An overview of the FVIII inhibitor incidences in studies of Jivi is provided in Table SVII-5.

Table SVII-5: Incidence of FVIII inhibitor development in Jivi studies

Study Number	Design	Treatment	Patients	Incidence of FVIII inhibitors
				Total n/N (%)
13401	Open-label, parallel group, phase 1	Prophylaxis	PTPs	0/14 (0.0)
13024	Open-label, partially randomised, phase 2/3	Prophylaxis	PTPs	0/114 (0.0)
		On-demand	PTPs	0/20 (0.0)
		Surgery	PTPs	2/14 (14.3)[a]
13024 extension	Optional, Open-label extension of SN 13024	Prophylaxis	PTPs	1/107 (0.9)[b]
		On-demand	PTPs	0/14 (0.0)
		Surgery	PTPs	0/20 (0.0)
15912	Open-label, phase 3	Prophylaxis	PTPs	0/73 (0.0)
15912 extension	Optional, open-label extension of SN 15912	Prophylaxis	PTPs	3/59 (5.1)[c]
21824 (Part A)	Open-label, Phase 3	Prophylaxis	PTPs	0/35 (0.0)
19764	Open-label, Phase 4	Prophylaxis	PTPs	0/32 (0.0)

[a] In one patient the positive inhibitor result was considered unconfirmed and transient; the other patient was considered to have a pre-existing FVIII inhibitor.
[b] In one patient the positive inhibitor result was considered unconfirmed and transient
[c] During the extension part in three patients the positive inhibitor result was transient, as all follow-up tests were negative.
n: Number of Patients; N: Total Number of Patients in The Population; PTPs: Previously Treated Patients; SN: Study Number; %: Percent.

Literature data (summarised in Table SVII-6 below) from studies of BDD-rFVIII in PTPs and PUPs show low inhibitor development in PTPs, and similar inhibitor development in PUPs as compared with FL-FVIII. Overall, the incidence of inhibitor development for all rFVIII concentrates (FL as well as BDD) ranges between 15% and 32% for PUPs and between 0.9% and 2.9% for PTPs (139).

Only one recent publication (a meta-analysis) reported a 7-fold higher incidence of inhibitor development for BDD-rFVIII compared with FL-rFVIII (140); however, the validity of this meta-analysis was questioned due to issues concerning the study design itself (141, 142).

For further details see **SVII.3.1.1 Background incidence/prevalence** and Table SVII-6 below.

Table SVII-6: Overview of incidence of inhibitor development with BDD-rFVIII according to the recent literature

Authors, year	Patient type and number	Incidence of inhibitors (%)	
		PUPs	PTPs
All rFVIII (FL-rFVIII, BDD-rFVIII)			
(139)	Review of epidemiological data	15–32%	0.9–2.9%
BDD-rFVIII			
(143)	17 PUPs 20 MTPs [< 50 EDs] 93 PTPs	17.6%	1.1%
(144)	101 PUPs	32%	N/A
(145)	113 PTPs	N/A	0.9%
(146)	204 PTPs	N/A	1.5%
(147)	16 PUPs 172 PTPs [>0 EDs]	18.7%	1.7%

BDD-rFVIII: B-domain-deleted recombinant FVIII; ED: Exposure Day; FL-rFVIII: Full-Length Recombinant FVIII; N/A: Not Applicable (respective population not enrolled); MTPs: Minimally Treated Patients; PTPs: Previously Treated Patients; PUPs: Previously Untreated Patients; <: Less than; ≥: Greater than; %: Percent.

Seriousness/outcomes

With regard to the pattern and patients' outcomes, inhibitors can be classified as transient (when they disappear without specific treatment) or non-transient. Table SVII-7 presents an overview of the patterns and outcomes of inhibitor development observed in clinical trials of Jivi.

Table SVII-7: Patterns and outcomes of FVIII inhibitor development in Jivi clinical studies

Study Number	Treatment	Transient inhibitors n/N (%)	Non-transient inhibitors n/N (%)	Outcome
13401	Prophylaxis	0/14 (0.0)	0/14 (0.0)	• N/A (no patients developed inhibitors)
13024	Prophylaxis	0/114 (0.0)	0/114 (0.0)	• N/A (no patients developed inhibitors)
	On-demand	0/20 (0.0)	0/20 (0.0)	• N/A (no patients developed inhibitors)
	Surgery	1/14 (7.1)	1/14 (7.1)[a]	• **Transient inhibitor**: patient underwent surgery and switched factor products in postoperative period. Testing 2 weeks later did not confirm the FVIII inhibitor. Patient resumed treatment with previous factor product and is reported to be doing well. • **Non-transient inhibitor**: Inhibitor was already present at screening (0.5 BU), and

Table SVII-7: Patterns and outcomes of FVIII inhibitor development in Jivi clinical studies

Study Number	Treatment	Transient inhibitors n/N (%)	Non-transient inhibitors n/N (%)	Outcome
				patient was known to have reduced FVIII recovery and half-life prior to enrolment; local pharmacokinetics obtained with the first exposure to Jivi showed reduced recovery and half-life. Patient underwent planned surgery using study drug, subsequently developed haematoma and underwent second surgery to evacuate haematoma (using study drug). After second surgery (inhibitor 0.7 BU/mL), patient changed to another FVIII product; 7 weeks after switching, FVIII inhibitor titre of 2.7 BU/mL was detected
13024 ext.	Prophylaxis	1/107 (0.9)	0/107(0.0)	• After ED 169 FVIII inhibitor (1.4 BU/mL) was measured one day after surgery, but not confirmed in second sample (<0.2 BU/mL, ED 204).
	On-demand	0/14 (0.0)	0/14 (0.0)	• N/A (no patients developed inhibitors)
15912	Prophylaxis	0/61 (0.0)	0/61 (0.0)	• N/A (no patients developed inhibitors)
15912 ext.	Prophylaxis	3/59 (5.1)	0/59 (0.0)	• After ED 145 in a [redacted]-year-old patient an inhibitor (0.7 BU/mL) was measured. Repeated blood tests were negative for FVIII inhibitors (one month later 0.3 BU/mL and two months later, <0.2 BU/mL). Dose of study drug was not changed, and no specific action was taken for the event. • At a total of 140 cumulative ED, the factor VIII inhibitor level was 0.6 BU/mL in a [redacted]-year-old patient. The dose of study drug was not changed, and no specific action was taken. Re-tests were negative. No confirmed inhibitor • At the final extension visit (after ED 311), a [redacted]-year-old patient showed an inhibitor titer of 1.5 BU/mL. Five days later patient was doing well informed *via* telephone due to patient's holiday. Action taken with the study drug was not applicable as the patient had already completed his last study visit. Patient was switched to an available commercial Factor VIII (Advate). Four weeks later, repeated sample taken, patient's Factor VIII inhibitor level was

Table SVII-7: Patterns and outcomes of FVIII inhibitor development in Jivi clinical studies

Study Number	Treatment	Transient inhibitors n/N (%)	Non-transient inhibitors n/N (%)	Outcome
				<0.2 BU.
21824 (Part A)	Prophylaxis	0/35		• N/A (no patients developed inhibitors)
19764	Prophylaxis	0/32		• N/A (no patients developed inhibitors)

BU: Bethesda Units; ED: Exposure Days; n: Number of patients; N: Total number of patients in the population; N/A: Not Applicable; mL: Milliliter; Ext.: Extension Study; SN: Study Number; %: Percent; <: Less than.

Severity and nature of risk

According to the ISTH, inhibitors have been classified as high or low response based on the anamnestic response of the antibody to antigenic challenge. The antibody level (titre) that distinguishes high vs low response is 5.0 BU.

Table SVII-8 presents an overview of the severity of disease in patients who developed inhibitors in clinical studies of Jivi. None of the positive inhibitors were confirmed in the second blood sample.

Table SVII-8: Severity of FVIII inhibitor development in Jivi clinical studies

Study Number	Treatment	EDs at baseline	Inhibitor titre high n/N (%)	Inhibitor titre low n/N (%)	EDs at inhibitor detection
13401	Prophylaxis	≥150	0/14 (0.0)	0/14 (0.0)	N/A
13024	Prophylaxis	≥150	0/114 (0.0)	0/114 (0.0)	N/A
	On-demand	≥150	0/20 (0.0)	0/20 (0.0)	N/A
13024 ext.	Surgery	≥150	0/14 (0.0)	2/14 (14.3)	0 and 1
	Prophylaxis	NA	0/107	0/107	169
	On-demand	NA	0/14	0/14	N/A
15912	Prophylaxis	>50	0/61 (0.0)	0/61 (0.0)	N/A
15912 ext.	Prophylaxis	NA	0/59	3/59	140, 145, 311
21824	Prophylaxis	≥50	0/35 (0.0)	0/35 (0.0)	N/A
19764	Prophylaxis	≥150	0/32 (0.0)	0/32 (0.0)	N/A

ED: Exposure Day; Ext.: Extension Study; N.A.: Not Applicable; n/N: Number; %: Percent; SN: Study Number; ≥: Greater than or equal to.

Post-Marketing Surveillance

There have been two reports of new confirmed FVIII inhibitors with Jivi, both of which occurred in adult patients. In one of the two cases transient low-titres FVIII inhibitors resolved while Jivi was maintained. In the second case the patient was switched to emicizumab and the inhibitor level decreased.

Background incidence/prevalence

It is generally agreed that inhibitor incidence should be presented for patients with severe haemophilia and presented separately for two distinct populations: PUPs (including or not including MTPs) and PTPs, since the expected incidence in these two groups is different. The most accepted figures for risk of inhibitor formation in patients with severe haemophilia range between 15% and 32% in PUPs/MTPs, while in PTPs this risk is about 0.9%-2.9% (139).

The incidence/prevalence of inhibitor formation is described in detail below.

In PUPs, the estimated incidence of inhibitor formation in patients with severe haemophilia mostly lies in the range 20%–30% (148) and the prevalence is about 15%. A review of epidemiological data on inhibitor formation (139) reported that the observed incidence of inhibitors in pivotal trial programmes for rFVIII products was in the range 15%–32% for PUPs and 0.9%-2.9% for PTPs. High titre inhibitors were detected in 10%–16% of PUPs and 0-2.3% of PTPs. Preliminary data from the EUropean HAemophilia Safety Surveillance (EUHASS) registry (149) reported inhibitor formation in 25% and 4% of PUPs with severe haemophilia A and severe haemophilia B, respectively. The incidence of inhibitors in PTPs with severe haemophilia A or B was < 0.1 to 0.6 per 100 patients per year.

In recent studies that involved children with severe haemophilia A, inhibitor development occurred at an average age of between one and two years after 9-12 treatments (150).

All FVIII products

In a study conducted in the UK, all patients with severe haemophilia were analysed for the age-adjusted occurrence of new FVIII inhibitors between 1990 and 2009. In 2,528 patients with severe haemophilia, 315 new inhibitors were found with the following incidence: 64.29 per 1,000 treatment-years in patients <5 years of age and 5.31 per 1,000 treatment-years at age 10-49 years, rising significantly to 10.49 per 1,000 treatment-years in patients more than 60 years of age. It was concluded that FVIII inhibitors arise in PWHA throughout life with a bimodal risk, being greatest in early childhood and in old age (151).

BDD-rFVIII

Available data show that inhibitors usually develop during the first 50 EDs to FVIII with the highest risk up to 20 EDs. It is a rare event past 100-150 EDs, but a low rate of inhibitor development has been documented through the sixth decade of life. Intensive FVIII treatment for surgery at first exposure leads to a higher inhibitor risk in haemophilia A patients compared with intensive treatment for bleeding (137).

In a 2003 workshop organised by the US Food and Drug Administration (FDA), data presented on spontaneous reports to the manufacturers of rFVIII products suggested that the inhibitor incidence might be higher in PTPs receiving BDD-rFVIII than in those receiving FL-rFVIII (152). However, the frequency of inhibitor development was similar with BDD-rFVIII and FL-FVIII in the most recent relevant literature, except for a meta-analysis which will be discussed at the end of this sub-section (140).

A review of early studies of BDD-rFVIII reported no inhibitor development in PTPs and a low incidence of inhibitor development in PUPs (14%; 10/72), with a median of 9.5 EDs until inhibitor detection (153). Also, in a prospective clinical study, inhibitor development to BDD-rFVIII (r-VIII SQ) was observed in one patient out of 113 PTPs with severe haemophilia A (0.9%). Inhibitor development was seen after 93 EDs and three years in this study (154).

Three multicentre clinical studies were conducted to evaluate the safety and haemostatic efficacy of BDD-rFVIII in PUPs or PTPs (155). In a pivotal trial of ReFacto (a BDD-rFVIII product manufactured in an albumin-free cell culture process) in 101 PUPs with severe haemophilia (144), the incidence of inhibitor development was 32% (32/101) after a median of 12 EDs (range 3-49 EDs), while the prevalence was 8% (8/101) with or without immune tolerance induction (ITI) (156). In a pivotal trial of ReFacto in 113 PTPs, only one patient (0.9%) developed inhibitor to FVIII after 113 EDs (145). In a randomised, double-blind, PK cross-over study in PTPs (146), the observed incidence of BDD-rFVIII inhibitor was 2.1% (2/94) in the intent-to-treat population and 2.2% (2/89) in the per protocol population restricted to patients with ≥50 EDs. In the following open-label, 6-month efficacy and safety study (n = 110), 1 case (0.9%) of *de novo* inhibitors and 2 cases (1.8%) of recurrent inhibitors were observed.

Findings in 130 Italian ReFacto users showed that after almost a year since commercial launch, ReFacto had induced inhibitor development in 1.1% of PTPs and 17.6% of PUPs (143). An interim report of a 5-year-long post-marketing surveillance study presented data on *de novo* inhibitors to ReFacto from German and Austrian centres. *De novo* inhibitors occurred in 6/188 (3.2%) patients with severe haemophilia, including 3/16 (18.7%) PUPs and 3/172 (1.7%) PTPs (defined as >0 EDs at baseline; 1 PTP was heavily pretreated with 51-100 EDs at baseline) (147).

All recently available data with BDD-rFVIII in PTPs or PUPs show low inhibitor development in PTPs, and similar inhibitor development in PUPs as compared with FL-FVIII. Overall, the available studies indicate that inhibitor development to BDD-rFVIII occurs in PTPs in a range of 0-1.7% and in PUPs in a range of 14-32%. Furthermore, these data show that inhibitors against BDD-rFVIII develop after 93-113 EDs in PTPs and after 3-49 EDs in PUPs.

Only one recent publication (140) was not in line with all the other analysed references and showed a marked increase of inhibitor incidence in PTPs who received BDD-rFVIII. In particular, the risk of any *de novo* inhibitors were 7-fold greater in patients exposed to BDD-rFVIII than in those exposed to FL-rFVIII, whereas high titre *de novo* inhibitors were 11-fold more likely. However, the validity of this meta-analysis may be questioned owing to

issues concerning the study design (141, 142). The results of this meta-analysis carry a high degree of statistical instability and uncertainty (e.g., the CIs of the HRs are extremely wide) for all inhibitors, which could be due to the small number of total events despite the large number of patients included in the analysis. A major limitation of this study was the potential introduction of biases into the meta-analysis based on the nature of the prospective studies selected. For example, the selected studies were non-randomised, observational investigations. Even though they were all prospective studies, none compared different concentrates in the same cohort; they typically evaluated one rFVIII product in a single cohort and many of the studies did not have a control group, which makes the quantification and/or interpretation of confounding practically impossible. In addition, the reason for switching PTPs to BDD-rFVIII or FL-rFVIII could be related to patient characteristics that are associated with an increased risk for inhibitor development. Another form of bias that seems very likely in this meta-analysis is due to the loss to follow-up of patients. The main and most important observation that can be drawn from this meta-analysis is that the development of inhibitors in PTPs is a relatively rare event (the cumulative hazard was 1.25%, with a 95% CI as narrow as 0.63-1.88%) (140). The mechanisms for increased immunogenicity, if at all, resulting from B-domain deletion in the BDD-rFVIII construct are currently unknown.
The fact that all the remaining studies did not show any increased risk of inhibitor development further demonstrates that studies of inhibitor development need to be carefully designed.

Risk factors and risk groups

Risk factors

Widely accepted risk factors for inhibitor development to FL-FVIII are the severity of the FVIII gene defect, the prior number of EDs, haemophilia severity, ethnicity, genotype, inhibitor testing frequency, intensity of treatment and familial predisposition. Other risk factors are still under debate, such as the specific treatment regimen, age at first exposure, mode of administration, surgery, type of FVIII concentrate, concomitant vaccinations and extravasations during injection. The risk factors for inhibitor development with BDD-rFVIII seem to be similar to those for FL-rFVIII.

The risk factors for inhibitor development in PWHA are described in detail below along with supporting evidence from the literature.

Patient-related risk factors for inhibitor development in haemophilia A

Severity of disease

It has been established that severe haemophilia is associated with an increased risk of inhibitor formation (148). In particular, the interplay between severity of disease and previous FVIII treatment leads to a higher risk of inhibitor development in PUPs or MTPs with severe haemophilia than in PTPs with severe haemophilia (149). Patients with mild to moderate haemophilia A are rarely exposed to FVIII; therefore, they have a low risk of developing inhibitors. Nevertheless, this complication has been increasingly recognised in patients with mild to moderate haemophilia (PUPs) who need intensive treatment with FVIII, for example during surgery (137).

Occurrence of an inhibitor in mild haemophilia is considered a major clinical problem since it changes the bleeding phenotype from mild to severe. Nevertheless it was noted that inhibitors in patients with mild haemophilia might be transient and disappear spontaneously (157).

Ethnic group

It has been reported that the risk of FVIII inhibitor development is increased in the African or Hispanic population (138, 150).

Viel *et al.* showed that inhibitor status among African-Americans was associated with *F8* haplotypes that are rarely seen in Caucasians (158); however, this could be limited to the Sub-Saharan African population since Elmahmoudi *et al.* found that *F8* haplotype frequencies in Tunisian PWHA are almost similar to those in Caucasians (159). *F8* haplotypes in the Japanese population show similarity to those in Caucasian populations (160).

Increased inhibitor prevalence was reported in the Hispanic population (138). An increased risk of inhibitor formation was also confirmed in patients with haemophilia who were of non-Caucasian ethnicity in a retrospective study (161). The relationship of genotype and race/ethnicity to history of inhibitor development was examined in a large cohort of patients with haemophilia in the US (162). There were no significant differences in mutation types and novel mutations across ethnicities. Nevertheless, inhibitor frequency was confirmed to differ by mutation type and race and was less frequent in Caucasian patients than in other patients.

No information about ethnic groups and risk of developing inhibitors to BDD-rFVIII is available.

Family history of antibodies to FVIII

In a cohort study of 113 haemophilia families, 69.9% were concordant in that either all or none of the siblings had a history of inhibitors. The mutation itself, with concordance of 42.4%, was not enough to predict the risk of therapy-induced inhibitor formation (163, 164). Differentiated data for family history of antibody development to BDD-rFVIII are not available.

Type of F8 mutation

A wide range of heterogeneous mutations in the gene coding for FVIII lead to partial or total deficiency of the protein activity. The type of mutation plays an important role as it can contribute to the prediction of risk of FVIII inhibitor formation, but is not the only determining factor (165). Severe or ‘null’ mutations (e.g., large deletions, nonsense mutations and intron-22 inversions) are associated with a higher risk of developing inhibitors and milder molecular defects (e.g., missense and splice site mutations) are associated with a lower risk for developing inhibitors (166). Eckhard *et al.* showed that an Arg593→Cys mutation in patients with mild to moderate haemophilia A is associated with a high-risk of inhibitor development under surgical conditions (136).

F8 gene mutations and ITI

A clinically proven strategy for achieving antigen-specific tolerance to FVIII in patients with inhibitors is immune tolerance induction (ITI), first reported by Brackmann *et al.* (167).

This procedure consists of the repeated high dose administration of FVIII concentrate in order to restore its efficacy, and in general it is performed with the same FVIII concentrate that triggered the appearance of inhibitors (168). According to a recent review (169), the impact of *F8* genotype on ITI outcome was examined in 86 patients in the Italian PROFIT study. A higher ITI success rate of 81% was noted in 16 patients with *F8* gene mutations predictive of a lower inhibitor risk, compared with a success rate of 47% in the remaining 70 patients with high-risk mutations. Although less significant than pre-ITI and ITI peak titres, *F8* genotype remained a predictor of ITI success in a multivariate analysis of this cohort.

Treatment-related risk factors for inhibitor development

Number of FVIII concentrate EDs

The risk of inhibitor development after FVIII treatment is greatest within the first 50 EDs, with the peak incidence during the first 20 EDs in PUPs (149). An increased risk of inhibitor development was shown in PUPs who were exposed to FVIII for at least three consecutive days in the setting of surgery or intensive treatment (137).

According to the available literature, the timing of inhibitor development in PUPs receiving BDD-rFVIII was in the range of 3-49 EDs; in several studies the median value was 12-14 EDs (144, 156, 170, 171). In PTPs, the timing of inhibitor development after use of BDD-rFVIII was in the range of 93-113 EDs (154), whereas a meta-analysis of clinical studies of FL- and BDD-rFVIII found that 63% of inhibitors developed before 40 EDs, with the latest occurrence being at 204 EDs (140).

Early age at first exposure to FVIII concentrates

The risk of inhibitor formation seems to be higher among patients with haemophilia initiating therapy before the age of 6 months than in those initiating therapy at a later age (172, 173). However, other studies found no significant difference in children treated at different time points during the first year of life (174, 175). In a retrospective case-control study in children with severe haemophilia, no association was shown between inhibitor development and age at first FVIII exposure (161). Commencing prophylaxis before 35 months of age was even regarded as a protective factor against development of inhibitors in children in a univariate analysis, and after adjustment for genetic and environmental risk factors in a multivariate analysis (176). According to the “danger theory” of tolerance (177), prophylaxis may offer a protective effect in the absence of other danger signals, whereas therapy on-demand may be perceived as dangerous due to danger signals from ongoing bleeding episodes (178).

According to recent findings, ideal prophylaxis and time of initiation in children has not yet been determined. Auerswald *et al.* suggested that low dose prophylaxis initiated before the first life year is associated with protection from inhibitors (179). Ragni *et al.* suggested that the optimal age to start a study to prevent inhibitor formation in children without previous bleeding is between four and seven months (180).

In patients with mild haemophilia, the risk of inhibitor formation is higher with increasing age, probably because of co-morbidities requiring surgical interventions and exposing these patients to an increased risk of inhibitor development (181).

Risk of inhibitor formation concerning BDD-rFVIII at an early age is not well characterised.

Type of FVIII product used

FVIII

Wight and Paisley carried out a review of the epidemiology of inhibitors in haemophilia A with respect to pdFVIII and rFVIII (148). The cumulative risk in PUPs treated with different plasma-derived products of low or intermediate purity was reported to range from 20.3% to 33.0%. By contrast, for patients treated with a single plasma-derived concentrate, the cumulative risk ranged from 0.0% to 12.4%. The cumulative risk for patients treated with a single recombinant product was reported to range from 36.0% to 38.7%. Together with the data described above, these results indicate that the analysis of concentrate immunogenicity is complicated by several factors related to the study design, the type, purity and number of the FVIII concentrate used, and the risk factors of the study population (39).

A meta-analysis (74) compared the incidence of inhibitor development in PUPs with haemophilia A treated with either pdFVIII or rFVIII. A total of 2,094 patients (1,965 treated with pdFVIII and 887 treated with rFVIII) from 224 studies were investigated. 420 patients developed inhibitors, which gave a pooled incidence of 14.3% for pdFVIII and 27.4% for rFVIII. High titre or high responding inhibitor (defined by an inhibitor titre ≥5 BU) incidence for pdFVIII and rFVIII was calculated to be 9.3% and 17.4%, respectively. This retrospective analysis points towards a higher incidence of FVIII inhibitor development in PUPs when treated with rFVIII products compared with pdFVIII products. However, this effect became progressively less pronounced when all inhibitors, high responding inhibitors or non-transient inhibitors were analysed. In the sensitivity and multivariate analysis, retrospective studies overestimated the inhibitor rate; thus, the inhibitor testing frequency, together with the study period and follow-up duration, can account for a significant portion of the variability found in inhibitor detection rate between pdFVIII and rFVIII products.

A survey of the EHTSB pointed out that no evidence is currently available for an association of inhibitor development in PTPs with product type or switching among products (182). Two retrospective studies published in 2010-2011 (161, 183) also concluded that the type of FVIII replacement product did not influence inhibitor development nor did switching from one product to another. In analyses of the clotting factor products used in Japanese patients with haemophilia (184), the incidence of inhibitor formation did not differ significantly between the group treated with plasma-derived products (29.7%) and the group treated with recombinant products (25.0%). These results suggest that the type of clotting factor preparation used for therapy has not influenced the incidence of inhibitor formation.

Franchini *et al.* evaluated the risk of inhibitor development with pdFVIII and rFVIII products using data from 25 prospective trials of 800 PUPs with severe haemophilia A (185). Overall, the inhibitor incidence did not differ significantly between recipients of pdFVIII and rFVIII concentrates. The main conclusion of this systematic review performed using selective criteria was that the type of FVIII product (i.e., pdFVIII vs rFVIII concentrates) does not seem to influence the inhibitor rate in PUPs with severe haemophilia A. The authors

explained the difference in their findings, especially compared with the results published by Iorio *et al.* (74), as being due to their selection of trials with high levels of quality and control.

The Survey of Inhibitors in Plasma-Product Exposed Toddlers (SIPPET) indicated that patients treated with plasma-derived FVIII containing vWF had a lower incidence of inhibitors than those treated with recombinant FVIII in PUPs (186).

Taken together, the data described above clearly do not point unequivocally in one direction. Results of meta-analyses need to be interpreted with great caution. The main limitations of meta-analyses and comparisons between clinical trials comprise the selection of the studies and differences in design, population, inhibitor detection and assay sensitivity. With regard to the latter, quite large variances in inhibitor detection have been reported between laboratories which have tested identical material (187). This might have an impact on the classification of patients as high or low responders. Hence, available data on the risk of inhibitor formation with different FVIII products are still inconclusive.

BDD-rFVIII: BDD-rFVIII demonstrated the same toxicity and immunogenicity profile as pdFVIII (Octanativ M) (153). Newly available studies compared the inhibitor development associated with FL-rFVIII and BDD-rFVIII concentrates. As described above, no difference in inhibitor development was measured in PTPs and PUPs, as inhibitor development was always low in PTPs (see also **Section SVII.3.1.1 Background incidence/prevalence**).**Section SVII.3.1.1 Background incidence/prevalence**.

Intensive exposure to FVIII product

Peak treatment periods (e.g., increased frequency and dose in surgery) may lead to an increased risk of inhibitor formation (171, 174). Kurnik *et al.* evaluated the impact of treatment intensity (median individual dose administered during the first six to eight weeks) and type of FVIII (recombinant or plasma-derived) on the risk of inhibitor development in PUPs with severe haemophilia (188). High titre inhibitors developed in 30/150 children (20%). Univariate analysis showed that a median dose increase per IU/kg body weight significantly increased the hazards towards high titre inhibitor development. In multivariate analysis, treatment intensity adjusted for FVIII products and treatment period was independently associated with the development of inhibitors. These data support the hypothesis that inhibitor development is of multifactorial origin as well as showing that treatment intensity plays a major role.

Intensive treatment was also shown to be a risk factor for inhibitor formation in children (161) regardless of the timing of the high-intensity treatment.

Surgical procedures

FVIII: Surgery in combination with intensive FVIII treatment in PWHA appears to be associated with inhibitor development, compared with intensive treatment for bleeding or prophylaxis alone. This association was particularly strong in PUPs for whom surgery was the reason for first treatment with FVIII (137). Inhibitor development was mainly observed in PUPs and in patients with mild to moderate haemophilia, during intensive factor exposure

and/or surgical situations. PTPs were not shown to have an increased incidence of inhibitors in these studies (189-192).

Since patients with mild haemophilia rarely receive prophylactic treatment, the development of inhibitors in these patients is an infrequent complication, which often occurs after intensive FVIII exposure for surgery. In particular, the risk of inhibitor formation in patients with mild haemophilia A is higher with increasing age and in patients with an Arg593→Cys mutation (181).

A review of case reports and open-label trials for the time period 1990–2001 reported that continuous infusion with FVIII was in general well tolerated (193). In a systematic review of the use of rFVIII continuous infusion in studies published between 2000 and 2006 (194), inhibitor development was reported in 1.9% of patients receiving continuous infusion with FVIII (in 5 of 258 patients in 3 of 11 comprehensive studies). In a study of safety and efficacy of a plasma-derived monoclonal FVIII concentrate during 10 years of follow-up (195), no inhibitor development occurred in 68 cases of surgery using continuous infusion; most patients were PTPs.

Eckhardt *et al.* conducted the first cohort study on the aetiology of inhibitors in patients with mild or moderate haemophilia (136). The results of this study suggested that intensive perioperative FVIII (especially when delivered by continuous infusion) in patients with mild to moderate haemophilia A carrying an Arg593→Cys mutation is a risk factor for the development of inhibitors. A systematic review investigated intensive FVIII treatment for surgery (137) and concluded that first exposure with intensive FVIII treatment for surgery leads to a higher inhibitor risk in PWHA than intensive treatment for bleeding. In this review, surgery was associated with a 2-fold increased risk of inhibitor development compared with prophylaxis. The limitation of this meta-analysis is the inclusion of observational, non-randomised studies, many without a control group, that are inappropriate for investigating or making inferences about causal effects. However, an association was detectable between inhibitor development and surgery, particularly when surgery was the reason for the first treatment with FVIII. Based on the limited data available in PTPs and surgeries with high dose and/or continuous infusion, no increased risk for PTPs undergoing surgeries is currently considered.

BDD-rFVIII: Data on the occurrence of inhibitor development after intensive exposure to BDD-rFVIII during surgery are scarce. In a study of the safety and efficacy of BDD-rFVIII in 38 PWHA, both previously treated and untreated (196), it was demonstrated that BDD-rFVIII was effective and had a favourable safety profile. Courter and Bedrosian evaluated 113 PTPs who received on-demand and/or prophylactic treatment with BDD-rFVIII, including treatment during surgery (145). The efficacy of administering BDD-rFVIII in conjunction with surgery was assessed to be “very useful” or “useful” in all cases. Few AEs were reported, and only 1 patient developed inhibitors to FVIII. In a retrospective study of 16 PTPs undergoing surgery and treated with BDD-rFVIII (ReFacto) *via* continuous infusion, Stieltjes *et al.* reported no inhibitor development among the AEs (197). It is not clear whether no inhibitor development occurred or whether this was not included in the safety assessment. In a more recent prospective study of 30 patients with severe or moderate haemophilia A who

were undergoing major elective surgery (198), the safety and efficacy of BDD-rFVIII (Xyntha) used *via* continuous infusion or BI were similar to the safety and efficacy of FL-rFVIII. One patient developed low-titre FVIII inhibitors.

Switch between FVIII products

FVIII: Switching from pdFVIII to rFVIII in adult PTPs in the context of an immunological challenge was considered to increase the risk of inhibitor formation (199). However, several other studies did not support the hypothesis that switching between FVIII product brands increases inhibitor risks in PTPs (170, 200-203).

The Concerted Action on Neutralizing Antibodies in severe haemophilia A (CANAL) study analysed the relative risk amongst the subset of patients who switched between product brands for the first time during the study period (n = 104) compared with those who stayed on their primary product (170). The results showed no increased inhibitor risk for the switching patients. This analysis included patients who had switched between recombinant or plasma-derived brands, as well as those who had switched brands within a category. The same results were obtained in a retrospective study of 118 patients with haemophilia: after the switch from pdFVIII to rFVIII, no *de novo* inhibitor development was observed. In addition, the safety and efficacy of pdFVIII and rFVIII products were similar (183).

A recent retrospective study evaluated 113 Irish patients (most of them with severe haemophilia) who switched from their FVIII treatment to a plasma- and albumin-free rFVIII (Advate). No inhibitor recurrence was observed in 16 of 17 patients with a history of inhibitors; one child had inhibitor recurrence. Only one of 96 patients with no previous inhibitor history developed de novo inhibitors. This patient was a child with three previous EDs and overall 6 EDs at the time of inhibitor diagnosis (204).

BDD-rFVIII: In a clinical study, 25 patients with severe haemophilia A who had at least 50 previous EDs to other FVIII concentrates switched to BDD-rFVIII. One patient had been treated with plasma-derived concentrates for decades before shifting to BDD-rFVIII and had no previous history of inhibitor development. In this patient, transient inhibitors (4%, 1/25) to BDD-rFVIII developed (205). In a retrospective study, PTPs who switched to BDD-rFVIII showed a low incidence of inhibitor development (205). In a retrospective analysis of patients with severe haemophilia A who were switched from a FL-rFVIII to a BDD-rFVIII and then back to a FL-rFVIII (206), only one patient out of 33 receiving significant exposure to BDD-rFVIII developed low-titre inhibitors.

Moreover, the WFH Guidelines for the management of haemophilia (3rd edition) state that for patients with haemophilia A who switch to another type or brand of factor product, the WFH has no preference for the choice of specific type of therapy, as current evidence indicates product switching does not increase risk of inhibitor development (207).

Risk groups

A few risk groups recognised for FVIII are discussed below.

PUPs *vs.* PTPs

Patients with haemophilia can be classified in subgroups with a different risk of inhibitor formation.

In patients who had never or rarely received any FVIII products (PUPs), inhibitors can develop relatively frequently in 15-32% (high titre: 10-16%) of cases (139), depending on risk factors such as the extent of the F8 gene defect. These patients are typically newborns and toddlers, whose immune system has not been exposed to endogenous FVIII epitopes during immune maturation, and who mount an allotypic antibody response to the exogenously administered FVIII.

In patients who have been treated for a long time with human FVIII products without complications (PTPs with more than 100 [EMA Pharmacovigilance {PV} Guidance] or more than 150 [ISTH] EDs), the risk for inhibitor development is low. These patients typically span all ages from young children with regular prophylactic infusions to adults with severe haemophilia A and episodic, on-demand treatment. The frequency of inhibitor formation in PTPs is between 0.9% and 2.9% (high titre: 0-2.3%) (139) and may be indicative of either temporary immune disturbance of the patient (e.g., following extensive surgery) or of neo-immunogenicity of the FVIII product. An increased incidence of inhibitor formation was reported in PTPs in the early 1990s after a process change for a pdFVIII product used in Belgium, the Netherlands and Germany. This experience, which was not predicted by preclinical investigations, has demonstrated the clear need for a proactive surveillance of inhibitor formation with any human FVIII product (208).

The PTP population has been considered the adequate population to study immunogenicity of a new FVIII product.

Untreated patients and risk of inhibitor development under surgery

The association between intensive FVIII exposure during surgery and inhibitor development is particularly strong in PUPs for whom surgery is the reason for first treatment with FVIII (137, 161, 171). With respect to BDD-rFVIII, PTPs showed a very low risk, if any, for inhibitor formation during surgery (145, 197). In a recent prospective study of patients with severe or moderate haemophilia treated with BDD-rFVIII for elective surgery, one out of 30 patients developed low-titre FVIII inhibitors (198).

Potential mechanisms

Inhibitors are the result of an allotypic immune response against exogenous FVIII replacement therapy (209, 210). The immune system on initial exposure to the infused clotting factor identifies it as a “foreign” protein. Generally, patients with severe haemophilia A are not tolerised to functional FVIII. This will result in a certain percent of inhibitory antibody development in this patient population. Inhibitory antibodies develop over the course of FVIII infusions from the activation of FVIII-specific B-cells, a subset of which

develops into memory B cells (211, 212). Establishment of the B-cell memory pool is in turn dependent on CD4+ T-helper cells that recognise FVIII-derived peptides presented on major histocompatibility complex (MHC)-II molecules by antigen-presenting cells (APCs), including macrophages and dendritic cells (DCs) (213-215). Upon activation by APCs, T-helper cells secrete cytokines such as interleukin (IL)-4, interferon (IFN)-γ, and transforming growth factor-β1 that support the differentiation and long-term maintenance of B cells expressing anti-FVIII antibodies (216-218). Hence the initial step in the immune cascade towards antibody production is the internalisation of FVIII by APCs for processing and presentation to T cells.

Preventability

In completed studies, no inhibitor development has been observed in PTPs receiving prophylaxis or on-demand treatment. Two non-confirmed, transient cases were observed in surgery patients. Two cases were reported from the post-marketing experience (as described above).

Some evidence suggests that continued prophylaxis treatment with replacement FVIII can prevent inhibitor formation in previously untreated young children with haemophilia A (171, 179).

Impact on individual patient

The development of antibodies to FVIII with neutralising properties (known as FVIII inhibitors) may have a great impact on treatment of patients with haemophilia. Therefore, inhibitor development is considered a medically significant event, and it is regarded as the most serious complication of FVIII replacement in patients with haemophilia. Inhibitors complicate haemophilia A treatment by making haemostatic management of bleeding events more difficult. Regular FVIII replacement may not be as effective, and these patients may need “bypassing” therapy, acting in different pathways of the coagulation system, for management of their bleeding events. These patients are also at a greater risk for the development of arthropathy, and they incur higher treatment costs as well as a higher use of medical resources to improve their quality of life.

Complex interplay exists between host genetic factors (patient-related risk factors) and circumstances involved in the treatment environment (treatment-related risk factors), which are critical contributory elements to inhibitor development. At present, it is not known whether the most important determinants for inhibitor formation are endogenous factors, previous low exposure, high exposure to FVIII for a short period, intensive exposure during surgery, switch to higher purity and rFVIII, or the mode of factor administration.

The approach for patients with FVIII inhibitors may vary depending on inhibitors response and whether the aim of the treatment is on-demand (during a bleeding episode or a surgical procedure) or prophylactic. For low-responding inhibitors (<5 BU/mL), the use of FVIII is preferred in a dose adapted according with the antibody titer for acute bleeds. For acute bleeds in patients with high-response inhibitors (≥5 BU/mL) a bypassing agent (recombinant activated FVII [rFVIIa] or activated prothrombin complex concentrate [aPCC]) or porcine FVIII should be used.

For prophylaxis in patients with hemophilia A who develop persistent low-responding inhibitors, the WFH suggests to consider the ITI (refer SVII.3.1.1-Sub header: Factor 8 gene mutations and ITI), which appears successful (persistent negative Bethesda titer, accompanied by normal PK, including factor recovery >66% and half-life >6 hours for SHL FVIII) in 70% to 80% of patients with severe hemophilia A. For patients with hemophilia A and persistent inhibitors who fail to ITI (or never underwent ITI), the use of emicizumab is recommended over bypassing agents (207).

Potential public health impact of safety concern

The development of inhibitors to FVIII can result in resistance to therapy and clinically significant bleeding.

There are very scarce data on the mortality risk attributed to inhibitors. In a Dutch cohort study of 967 patients with haemophilia (94 died; 2 lost to follow-up) followed for 8,868 patient-years, the authors were unable to study the impact of inhibitors on mortality because of the limited information on the presence of inhibitory antibodies in this population (24). In the Insight Study, mortality was analysed using the Cox regression model. Patients with inhibitors had an almost four-fold increase of all-cause mortality (adjusted HR 3.8; 2.1-6.8) as compared with patients without inhibitors. In half of the patients, cause of death was reported: malignancy (n = 19; 32%), viral infections (HIV and HCV; n = 16; 27%) or intracranial bleeding (n = 13; 22%) (219).

Evidence source

Refer to **Annex 7**.

Medical Dictionary for Regulatory Activities (MedDRA) terms

Searches of Preferred Terms (PTs) (MedDRA version 26.1): Acquired haemophilia with anti FVIII, XI, or XIII, Anti FVIII antibody increased, Anti FVIII antibody positive, Anti FVIII antibody test, Antibody test abnormal, Antibody test positive, Coagulation FVIII level abnormal, Coagulation FVIII level decreased, Coagulation factor decreased, Coagulation factor inhibitor assay, Drug effect decreased, Drug effect delayed, Drug effect incomplete, Drug effect variable, Drug half-life reduced, Drug ineffective, Drug ineffective for unapproved indication, Drug level below therapeutic, Drug level decreased, Drug resistance, Drug-specific antibody present, Drug tolerance, Drug tolerance increased. FVIII inhibition, Haemophilia A with anti FVIII, Inhibiting antibodies, Inhibiting antibodies positive, Inhibitory drug interaction, Neutralising antibodies, Neutralising antibodies positive, No reaction on previous exposure to drug, No therapeutic response, Non-neutralising antibodies, Therapeutic product ineffective, Therapeutic product ineffective for unapproved indication, Therapeutic response changed, Therapeutic response decreased, Therapeutic response delayed, Treatment failure.

SVII.3.1.2 Important identified risk: hypersensitivity

Frequency with 95% CI

Clinical trials (all clinical trial populations including open extension):

In order to ensure that all potential events of hypersensitivity were identified, broad MedDRA searches were conducted, and the individual cases reviewed to identify cases that could represent drug-related hypersensitivity events. Most of these events were not related to the study drug. Therefore, more specific MedDRA terms were used to identify hypersensitivity reactions that were drug related.

At the time of this RMP, four pivotal studies (SNs 13401, 13024, 15912, 21824 [Part A]), including the extension parts of SNs 13024 and 15912), and one phase 4 interventional study (SN. 19764) have been completed. The AE frequencies presented in the current RMP are taken from pooled data of these clinical trials, including the extension parts of SN 13024 and SN 15912.

Overall, treatment-emergent adverse events (TEAEs) potentially related to hypersensitivity reactions based on a MedDRA search for hypersensitivity symptoms occurred in 96 patients (40.0%) aged ≥7 years and 33 patients (68.8%) aged <7 years. No anaphylaxis was reported.

Among patients ≥7 years of age, the most frequently reported TEAEs (≥5%) potentially related to hypersensitivity reactions were headache (42 patients, 17.5%), cough (26 patients, 10.8%), nausea (14 patients, 5.8%) and vomiting (13 patients, 5.4%). Only eight patients (3.3%) experienced at least one TEAE possibly related to hypersensitivity that was drug related based on the investigator's assessment: cough (n = 1), dizziness (n = 1), drug hypersensitivity (n = 1), dyspnea (n = 1), erythema multiform (n = 1), headache (n = 2), hypersensitivity (n = 2), pruritus (n = 2), rash macular-papular (n = 1) (for some of the patients multiple events were reported). Three drug-related events led to discontinuation of Jivi: two of these drug-related cases with MedDRA PT "Drug Hypersensitivity" and "Hypersensitivity" (both in patients receiving Jivi as prophylaxis in SN 13024 - part A) led to discontinuation of Jivi after the first and fourth dose response. In addition, one drug-related case of hypersensitivity (reported in a patient receiving prophylaxis with Jivi in SN 19764) led to discontinuation of Jivi after 32 ED. No hypersensitivity events related to Jivi were reported in SN 21824 in children 7-<12 years of age.

Among patients <7 years of age, the most frequently reported TEAEs (≥5%) potentially related to hypersensitivity reactions were cough (16 patients, 33.3%), vomiting (10 patients, 20.8%), rash (seven patients, 14.6%), headache (six patients, 12.5%), hypersensitivity (five patients, 10.4%), nausea (four patients, 8.3%) asthma, conjunctivitis and urticaria (three patients each, 6.3%). Only five patients (10.4%) experienced at least one TEAE potentially related to hypersensitivity symptoms that was drug-related based on the investigator's assessment: cough (n = 1), drug hypersensitivity (n = 1) and hypersensitivity (n = 3). Four cases of drug hypersensitivity and hypersensitivity (all in patients receiving Jivi as prophylaxis in SN 15912) led to discontinuation of Jivi.

An overview of the incidence of hypersensitivity events in studies of Jivi is provided in Table SVII-9.

Table SVII-9: Incidence of AEs potentially related to hypersensitivity reactions (broad MedDRA search) in pooled analysis of Jivi SNs 13401, 13024 part A including extension part (excluding subjects enrolled for Part B only) SN 15912 (main part and part 2) and extension, SN 21824 (Part A) and SN 19764

Patients with at least one such AE possibly related to hypersensitivity, n (%)	Age ≥7 years (N = 240)	Age <7 years (N = 48)	Total (N = 288)
TEAE	96 (40.0)	33 (68.8)	129 (44.8)
Drug-related TEAE	8 (3.3)	5 (10.4)	13 (4.5)
Positive anti-PEG or anti-PEG IgM antibodies at time of TEAE (≤2 weeks)	1 (0.4)	6 (12.5)	7 (2.4)
TEAE leading to Jivi discontinuation	3 (1.3)	4 (8.3)	7 (2.4)
Drug-related TEAE leading to Jivi discontinuation	3 (1.3)	4 (8.3)	7 (2.4)

AE: Adverse Event; Ig: Immunoglobulin; n: Number of patients; N: Total number of patients in the population; PEG: Polyethylene Glycol; SN: Study Number; TEAE: Treatment-Emergent Adverse Event; <: Less than; ≤: Less than or equal to; ≥: Greater than or equal to; %: Percent.

Overall, in the pool of all patients receiving Jivi in clinical trials the majority of hypersensitivity events related to Jivi were reported within the first four EDs. There was only one report of drug hypersensitivity after the fourth ED: this adult participant in SN 19764 experienced mild cough during the first infusion and two episodes of mild hypersensitivity (characterized by shortness of breath and headache) on ED 31 and ED 32, Jivi was withdrawn. No cases of hypersensitivity related to Jivi were reported from SN 21824 (part A) conducted in children 7-<12 years of age.

Post-marketing Surveillance

A small number of hypersensitivity reactions to Jivi have been reported. The majority with known time-to-onset occurred within the first 4 ED. The reporting rate of hypersensitivity reactions to Jivi remains low and compatible with reporting in clinical trials.

Literature data on hypersensitivity from studies of BDD-rFVIII are not available yet.

Rare anaphylactic reactions have been reported in PWHA with exposure to either cryoprecipitate, low-purity FVIII concentrates, or immunopurified plasma-derived products or rFVIII concentrates (220-226).

No epidemiological data on incidence or prevalence of anaphylaxis in PWHA were identified. According to an epidemiological analysis of the French Medicines and Healthcare Products Regulatory Agency (*Agence française de sécurité sanitaire des produits de santé*, AFSSAPS) for the period 2000–2007 (227), reactions to blood components resembling allergy (including reactions to FVIII) represented 26.1% of all ARs. The incidence was 0.6/1,000 transfused blood components; there were 6 deaths (5.6%) during the same period.

Seriousness/outcomes

Generally, hypersensitivity reactions may cause a range of symptoms from minor inconvenience to fatal outcome (anaphylaxis). No cases of anaphylaxis were reported. Testing for IgE antibodies to PEG was negative in all patients.

Table SVII-10 and Table SVII-11 present seriousness, outcome, and symptoms potentially related to hypersensitivity reactions by MedDRA search that occurred in Jivi clinical studies.

Table SVII-10: Treatment-emergent serious drug-related hypersensitivity reactions in pooled analysis of Jivi SNs. 13401 and 13024 part A including extension part (excluding subjects enrolled for Part B only) and SN 15912 (main part and part 2) and extension, SN 21824 (Part A) and SN 19764

Patients with at least one such TESAE, n (%)	Age ≥7 years (N = 240)	Age <7 years (N = 44)	Total (N = 288)
TESAEs possibly related to hypersensitivity	1 (0.4)	4 (8.3)	5 (1.7)
Drug hypersensitivity	1 (0.4)[a]	1 (2.1)[a]	2 (0.7)[a]
Hypersensitivity	0	3 (6.3)[a]	3 (1.0)[a]

[a] Both patients with serious drug hypersensitivity and two of the three patients with serious hypersensitivity also had positive anti-PEG and/or anti-PEG IgM antibodies during the study.
N: Number of patients; N: Total number of patients in the population; SN: Study Number; TESAE: Treatment-Emergent Serious Adverse Event; <: Less than; ≥: Greater than or equal to; %: Percent

Table SVII-11: Outcome of AEs potentially related to hypersensitivity reactions (broad MedDRA search) in pooled analysis of Jivi SNs. 13401 and 13024 part A including extension part (excluding subjects enrolled for Part B only) and SN 15912 (main part and part 2) and extension, SN 21824 (Part A) and SN 19764

Patients with TEAEs possibly related to hypersensitivity by worst outcome, n (%)	Age ≥7 years (N = 240)	Age <7 years (N = 48)	Total (N = 288)
Total	96 (40.0)	33 (68.8)	129 (44.8)
Recovered/resolved	81 (33.8)	27 (56.3)	108 (37.5)
Recovering/resolving	2 (0.8)	2 (4.2)	4 (1.4)
Not recovered/not resolved	13 (5.4)	4 (8.3)	17 (5.9)

MedDRA: Medical Dictionary for Regulatory Activities; n: Number of patients; N: total number of patients in the population; SN: Study Number; TEAE: Treatment-Emergent Adverse Event; <: Less than; ≥: Greater than or equal to; %: Percent.

Treatment emergent drug-related hypersensitivity reactions were classed as serious in one patient aged ≥7 years and in four patients aged <7 years Table SVII-10. The majority of treatment-emergent possible hypersensitivity reactions were recovered/resolved in both age groups Table SVII-11. Details of patients with the PT “Drug hypersensitivity” or “hypersensitivity” reported as a serious TEAE are shown in Table SVII-12.

Part II: Module SVII - Identified and potential risks

Table SVII-12: Details of patients with the PT 'drug hypersensitivity' or 'hypersensitivity' reported as a TESAE in Jivi clinical studies13401, 13024 part A including extension part (excluding subjects enrolled for Part B only)) and 15912 (main part and part 2) and extension, SN 21824 (Part A) and SN 19764

Study/patient/age	Treatment/Timing related to drug administration	Hypersensitivity symptoms	Outcome
13024[redacted] [redacted] years	Prophylaxis/ Following the 4th infusion	Headache, abdominal pain, dyspnoea, and flushing	All symptoms resolved without the patient seeking medical intervention; patient later refused re-challenge and discontinued from study (Antibodies to Jivi and high titer anti-PEG IgM antibodies were detected 4 days after the event, but were negative one month later)
15912[redacted] [redacted] years	Prophylaxis/ Five minutes following the first infusion	Vomiting, sneezing and wheals	Treatment with steroids and anti-histamines; resolved 90 minutes later; patient discontinued from study (Antibodies to Jivi and PEG were not detected in this patient)
15912[redacted] [redacted] years	Prophylaxis/ Following the fourth infusion	Cough, dyspnoea, skin redness, vomiting, back pain, and drowsiness	No treatment: symptoms lasted 30 minutes; patient discontinued from study (Antibodies to PEG were detected at follow-up)
15912/[redacted] [redacted] years	Prophylaxis/ A few minutes following the third and fourth infusions	Flushing (3rd and 4th infusions) Fainting, hypotension; and desaturation (5th infusion)	Patient recovered over 10 minutes following the 3rd and 4th infusions. The 5th infusion was administered by the physician. Patient recovered over 15–20 minutes following AEs during 5th infusion; study drug was withdrawn (Antibodies to Jivi and high titer anti-PEG IgM antibodies with FVIII recovery of zero were detected at follow-up but were negative 2 months after last study drug exposure)

Table SVII-12: Details of patients with the PT 'drug hypersensitivity' or 'hypersensitivity' reported as a TESAE in Jivi clinical studies13401, 13024 part A including extension part (excluding subjects enrolled for Part B only)) and 15912 (main part and part 2) and extension, SN 21824 (Part A) and SN 19764

Study/patient/age	Treatment/Timing related to drug administration	Hypersensitivity symptoms	Outcome
15912[redacted] [redacted] years	Prophylaxis/ Immediately following the third infusion	Feeling dry, cough, pruritus with petechial exanthema	Patient discontinued from study. Positive result for anti-PEG IgM antibody at baseline, negative at time of second infusion, with increase in titre around time of reaction, when anti-Jivi and anti-PEG antibodies were also detected. Antibody results were negative at final visit three weeks later

min: Minutes; PT: Preferred Term; SN: Study Number; TESAE: Treatment-Emergent Serious Adverse Event; PEG: Polyethylene Glycol, IgM: Immunoglobulin M; %: Percent.

Severity and nature of risk

Hypersensitivity reactions are mostly mild or moderate in intensity and transient; they may involve skin (urticaria), eyes (conjunctivitis), nasopharynx, bronchopulmonary tissues and gastrointestinal tract. Depending on the severity and type of the reactions, they can be local or systemic.

Of the seven drug-related cases reported as "hypersensitivity" or "drug hypersensitivity", five cases (4 of them <7 years of age) were classified as SAEs and are presented in Table SVII-12. In four of these cases anti-PEG IgM antibodies were detected on the day of the hypersensitivity reaction or within four days after the reaction. Not all patients who develop anti-PEG IgM antibodies in response to administration of Jivi will develop hypersensitivity reactions. In those patients who present with symptoms temporally consistent with drug hypersensitivity, it is likely that the IgM-drug complexes activate complement which leads to their symptoms (228). None of these patients had anti-PEG IgE antibodies.

Table SVII-13 presents the maximum intensity of possible hypersensitivity reactions (by broad search of terms) that occurred in Jivi clinical studies.

Table SVII-13 : Maximum intensity of TEAEs possibly related to hypersensitivity reactions (broad MedDRA search) in pooled analysis of Jivi SNs. 13401, 13024 part A including extension part (excluding subjects enrolled for Part B only) and SN 15912 (main part and part 2) and extension, SN 21824 (Part A) and SN 19764

Patients with TEAEs possibly related to hypersensitivity by maximum intensity, n (%)	Age ≥7 years (N = 240)	Age <7 years (N = 48)	Total (N = 248)
Mild	68 (28.3)	20 (41.7)	88 (30.6)
Moderate	22 (9.2)	13 (27.1)	35 (12.2)
Severe	6 (2.5)	0	6 (2.1)
Total	**96 (40.0)**	**33 (68.8)**	**129 (44.8)**

MedDRA: Medical Dictionary for Regulatory Activities; n: Number of patients; N: Total number of patients in the population; SN: Study Number; TEAE: Treatment-Emergent Adverse Event; <: Less than; ≥: Greater than or equal to; %: Percent.

The majority of TEAEs possibly related to hypersensitivity (by broad MedDRA search of PTs possibly related to hypersensitivity) were of mild or moderate intensity. Six patients ≥7 years had a severe AE possibly related to hypersensitivity reaction. In one of these 6 patients the event “drug hypersensitivity” was classified as related to study drug and serious ([redacted] described in Table SVII-12. In the remaining five patients, the events were not considered related to Jivi.

Post-marketing Surveillance

The vast majority of hypersensitivity reactions reported from the post-marketing experience was non-serious.

Background incidence/prevalence

Skin associated hypersensitivity reactions are considered common with therapeutic proteins or monoclonal antibodies. Systemic hypersensitivity reactions are rare.

Anaphylactic reactions have been rarely reported in PWHA with use of either plasma-derived or rFVIII concentrates. There are no epidemiological data on PWHA. In an analysis of the AFSSAPS for the period 2000–2007 (227), reactions to blood components resembling allergy (including reactions to FVIII) represented 26.1% of all ARs. The incidence was 0.6/1,000 transfused blood components. A Swiss study estimated the incidence of severe systemic anaphylaxis in the general population, excluding hospital-acquired cases, at 8.4/100,000 person-years, and drug-induced anaphylaxis at 1.6/100,000 person-years (229). A Dutch study reported the incidence of anaphylaxis of any cause and drug-induced anaphylaxis to be 1.15 per 100,000 per year and 0.37 per 100,000 per year, respectively (230). A US study estimated the incidence of mild, moderate or severe anaphylaxis at 21/100,000 white people (231).

No data from studies regarding hypersensitivity reactions due to BDD-rFVIII are available.

The clinically relevant hypersensitivity reactions observed with Jivi occurred during or immediately following drug administration (Table SVII-12). These reactions are commonly referred to in the literature as infusion reactions. Infusion reactions have been reported with biological compounds across therapeutic areas. Anaphylaxis is rarely observed with most products.

Hypersensitivity reactions with Jivi that are associated with anti-PEG antibodies are IgM in isotype. While IgM antibodies have been detected in association with infusion reactions, the strong association between only an IgM isotype antibody and infusion reactions is less common.

Risk groups or risk factors

Age ≤6 years has been identified as a risk factor for hypersensitivity reactions associated with the development of anti-PEG antibodies to Jivi.

Potential mechanisms

Hypersensitivity reactions may be associated with the development of antibodies to FVIII, the PEG moiety or any of the components of Jivi. Anti-PEG IgM antibodies were detected in patients experiencing hypersensitivity reactions to Jivi. IgE antibodies were negative in all patients. No isotype switching to IgG has been observed. The absence of isotype switching indicates a T-cell independent mechanism. The production of exclusively IgM antibodies in response to a stimulus has been described with marginal zone B cells or the B-1b cell population. Following administration of Jivi, both hypersensitivity reactions and increasing titres of anti-PEG IgM antibodies leading to loss of efficacy occur primarily in young children <6 years of age. This suggests that the B-1b cell population which develops in utero is more likely to be responsible for the generation of the anti-PEG antibodies in response to Jivi administration.

Polyethylene glycol (PEG) consists of repeating subunits of ethylene glycol. These repeating units are likely being recognised by pattern recognition receptors of the innate immune system leading to the generation of anti-PEG IgM. Immune complexes of Jivi and anti-PEG IgM are able to activate complement. Complement activation can explain the symptoms reported as hypersensitivity reactions during or immediately following Jivi administration.

The B-1b cells undergo mutations in their immunoglobulin genes that approximate the adult before 6-7 years of age (232). These changes in the B-1b cells may be responsible for the low incidence of anti-PEG IgM generation following the administration of Jivi in adults.

Preventability

Since the generation of anti-PEG IgM antibodies in response to administration of Jivi is greatest in young children <6 years of age, excluding this population is the most effective method of prevention of hypersensitivity reactions. Since B-1b cells evolve towards the adult phenotype by approximately age 6-7 years (232), excluding all children <7 years minimizes the risk of hypersensitivity reactions to Jivi.

Some hypersensitivity reactions will occur to components of Jivi other than PEG. Therefore, Jivi is contraindicated in patients with known hypersensitivity to the active substance or any of its excipients, or in patients with known allergic reactions to mouse or hamster proteins.

The majority of hypersensitivity reactions have occurred within the first 4 administrations of Jivi. This temporal relationship enables healthcare providers to be especially vigilant regarding the potential for hypersensitivity reactions in association with the first 4 EDs.

In clinical studies of Jivi, patients are made aware of the early signs and symptoms of these reactions and instructed to contact their physicians if these signs occur.

Impact on individual patient

No specific analyses of quality of life were performed in the subgroup of patients with hypersensitivity reactions in the Jivi clinical trial programme. Development of hypersensitivity reactions to the administration of Jivi resulted in discontinuation of the product. These patients were able to resume their prior FVIII replacement product. The anti-PEG IgM antibody titres declined over time becoming negative weeks to months after discontinuation of Jivi. The antibodies are specific to Jivi. Therefore, there is expected to be limited or no cross-reactivity to other PEGylated therapeutics. In summary, the impact on the patient is likely to be moderate.

Potential public health impact of safety concern

Drug hypersensitivity to Jivi will result in discontinuation of therapy. There does not appear to be any impact on the efficacy of other FVIII replacement products. Since there are many available products for the treatment of Haemophilia A, no public health concern exists related to hypersensitivity reactions to Jivi.

Evidence source

Refer to **Annex 7**.

MedDRA terms

For the analyses presented in this section; AEs coded to a PT belonging to one of the following Standardised MedDRA Queries (SMQs) or selected PTs were considered to be AEs possibly related to hypersensitivity reactions (MedDRA Version 26.1):

- SMQ “Anaphylactic reactions” (SMQ 20000021, broad search)
- SMQ “Angio(o)edema” (SMQ 20000024, broad search)
- SMQ “Hypersensitivity” (SMQ 20000214)

PTs

AGEP-DRESS overlap, Acquired C1 inhibitor deficiency, Acute generalized exanthematous pustulosis, Acute respiratory failure, Administration related reaction, Administration site dermatitis, Administration site eczema, Administration site hypersensitivity, Administration site photosensitivity reaction, Administration site rash, Administration site recall reaction, Administration site urticarial, Administration site vasculitis, Airway remodeling, Allergic bronchitis, Allergic colitis, Allergic cough, Allergic cystitis, Allergic eosinophilia, Allergic

gastroenteritis, Allergic hepatitis, Allergic keratitis, Allergic lymphangitis, Allergic oedema, Allergic otitis externa, Allergic otitis media, Allergic pharyngitis, Allergic reaction to excipient, Allergic respiratory disease, Allergic respiratory symptom, Allergic sinusitis, Allergic stomatitis, Allergic transfusion reaction, Allergy alert test positive, Allergy test positive, Allergy to chemicals, Allergy to fermented products, Allergy to immunoglobulin therapy, Allergy to surgical sutures, Allergy to vaccine, Alpha tumor necrosis factor increased, Alveolitis, Anal eczema, Anaphylactic reaction, Anaphylactic shock, Anaphylactic transfusion reaction, Anaphylactoid reaction, Anaphylactoid shock, Anaphylaxis treatment, Angioedema, Anti-insulin antibody increased, Anti-insulin antibody positive, Anti-insulin receptor antibody increased, Anti-insulin receptor antibody positive, Anti-neutrophil cytoplasmic antibody positive vasculitis, Antiallergic therapy, Antibody test abnormal, Antibody test positive, Antiendomysial antibody positive, Antibody-dependent enhancement, Application site dermatitis, Application site eczema, Application site hypersensitivity, Application site photosensitivity reaction, Application site rash, Application site recall reaction, Application site urticarial, Application site vasculitis, Arthritis allergic, Aspirinexacerbated respiratory disease, Asthma, Asthma late onset, Asthma-chronic obstructive pulmonary disease overlap syndrome, Asthmatic crisis, Atopic cough, Atopy, Auricular swelling, Blepharitis allergic, Blister, Blister rupture, Blood immunoglobulin A abnormal, Blood immunoglobulin A increased, Blood immunoglobulin D increased, Blood immunoglobulin E abnormal, Blood immunoglobulin E increased, Blood immunoglobulin G abnormal, Blood immunoglobulin G increased, Blood immunoglobulin M abnormal, Blood immunoglobulin M increased, Blood pressure decreased, Blood pressure diastolic decreased, Blood pressure systolic decreased, Bone cement allergy, Breast oedema, Breast swelling, Bromoderma, Bronchial hyperreactivity, Bronchial oedema, Bronchospasm, Bullous hemorrhagic dermatosis, Bullous impetigo, Caffeine allergy, Capillaritis, Cardiac arrest, Cardio-respiratory arrest, Cardio-respiratory distress, Cardiovascular insufficiency, Catheter site dermatitis, Catheter site eczema, Catheter site hypersensitivity, Catheter site rash, Catheter site urticarial, Catheter site vasculitis, Charcot-Leyden crystals, Cheilitis, Chest discomfort, Childhood asthma, Chills, Choking, Choking sensation, Chronic eosinophilic rhinosinusitis, Chronic hyperplastic eosinophilic sinusitis, Circulatory collapse, Circumoral oedema, Circumoral swelling, Complement factor C1 decreased, Complement factor C2 decreased, Complement factor C3 decreased, Complement factor C4 decreased, Complement factor decreased, Conjunctival oedema, Conjunctivitis, Conjunctivitis allergic, Contact stomatitis, Contrast media allergy, Contrast media reaction, Corneal exfoliation, Corneal oedema, Cough, Cough variant asthma, Cross sensitivity reaction, Cutaneous vasculitis, Cyanosis, Cytokine increased, Cytokine release syndrome, Cytokine storm, Dennie-Morgan fold, Dermal filler reaction, Dermatitis, Dermatitis acneiform, Dermatitis allergic, Dermatitis atopic, Dermatitis bullous, Dermatitis contact, Dermatitis exfoliative, Dermatitis exfoliative generalized, Dermatitis herpetiformis, Dermatitis infected, Dermatitis psoriasiform, Device allergy, Dialysis membrane reaction, Diastolic hypotension, Distributive shock, Dizziness, Documented hypersensitivity to administered product, Drug eruption, Drug hypersensitivity, Drug provocation test, Drug reaction with eosinophilia and systemic symptoms, Dyspnoea, Ear swelling, Eczema, Eczema infantile, Eczema nummular, Eczema vaccinatum, Eczema vesicular, Eczema weeping, Encephalitis allergic, Encephalopathy allergic, Endotracheal

intubation, Enhanced respiratory disease, Eosinophil count abnormal, Eosinophil count increased, Eosinophil percentage abnormal, Eosinophil percentage increased, Eosinophilia, Eosinophilia myalgia syndrome, Eosinophilic angiocentric fibrosis, Eosinophilic bronchitis, Eosinophilic granulomatosis with polyangiitis, Eosinophilic esophagitis, Eosinophilic pneumonia, Eosinophilic pneumonia acute, Eosinophilic pneumonia chronic, Epidermal necrosis, Epidermolysis, Epidermolysis bullosa, Epiglottic oedema, Erythema, Erythema multiforme, Erythema nodosum, Exfoliative rash, Eye allergy, Eye oedema, Eye pruritus, Eye swelling, Eyelid oedema, Face oedema, Fixed eruption, Flushing, Foreskin oedema, Gastrointestinal oedema, Generalized bullous fixed drug eruption, Generalized oedema, Genital rash, Genital swelling, Giant papillary conjunctivitis, Gingival oedema, Gingival swelling, Gleich's syndrome, Godet's sign positive, HLA marker study positive, Hemolytic transfusion reaction, Hemorrhagic urticarial, Hand dermatitis, Headache, Henoch-Schonlein purpura, Henoch-Schonlein purpura nephritis, Heparin-induced thrombocytopenia, Hereditary angioedema, Hereditary angioedema with C1 esterase inhibitor deficiency, Hereditary angioedema with normal C1 esterase inhibitor, Human anti-hamster antibody increased, Human anti-hamster antibody positive, Hypersensitivity, Hypersensitivity myocarditis, Hypersensitivity pneumonitis, Hypersensitivity vasculitis, Hyperventilation, Hypotension, Hypotensive crisis, Idiopathic angioedema, Idiopathic histaminergic angioedema, Idiopathic urticarial, Immediate post-injection reaction, Immune complex level increased, Immune thrombocytopenia, Immune tolerance induction, Immunoglobulins abnormal, Immunoglobulins increased, Immunology test abnormal, Implant site dermatitis, Implant site hypersensitivity, Implant site photosensitivity, Implant site rash, Implant site urticarial, Incision site dermatitis, Incision site rash, Infusion related hypersensitivity reaction, Infusion related reaction, Infusion site dermatitis, Infusion site eczema, Infusion site hypersensitivity, Infusion site photosensitivity reaction, Infusion site pruritus, Infusion site rash, Infusion site recall reaction, Infusion site urticarial, Infusion site vasculitis, Injection related reaction, Injection site dermatitis, Injection site eczema, Injection site hypersensitivity, Injection site panniculitis, Injection site photosensitivity reaction, Injection site rash, Injection site recall reaction, Injection site urticarial, Injection site vasculitis, Instillation site hypersensitivity, Instillation site rash, Instillation site urticarial, Interstitial granulomatous dermatitis, Interstitial lung disease, Intestinal angioedema, Iodine allergy, Irregular breathing, Kounis syndrome, Laryngeal dyspnea, Laryngeal obstruction, Laryngeal oedema, Laryngitis allergic, Laryngospasm, Laryngotracheal oedema, Lethargy, Leukotriene increased, Limbal swelling, Lip exfoliation, Lip oedema, Lip swelling, Localized oedema, Macrophage inflammatory protein-1 alpha increased, Mast cell activation syndrome, Mast cell degranulation present, Mechanical urticarial, Medical device site dermatitis, Medical device site eczema, Medical device site hypersensitivity, Medical device site photosensitivity reaction, Medical device site rash, Medical device site recall reaction, Medical device site urticarial, Mesenteric panniculitis, Monocyte chemotactic protein-2 increased, Mouth swelling, Mouth ulceration, Mucocutaneous rash, Mucocutaneous ulceration, Mucosa vesicle, Mucosal erosion, Mucosal exfoliation, Mucosal necrosis, Mucosal ulceration, Multiple allergies, Multiple drug hypersensitivity, NSAID exacerbated respiratory disease, Nasal crease, Nasal obstruction, Nasal oedema, Nausea, Necrotizing panniculitis, Nephritis allergic, Neurodermatitis, Neutralizing antibodies positive, Nikolsky's sign, Nipple oedema, Nipple swelling, Nodular

rash, Non-neutralizing antibodies positive, Noninfective conjunctivitis, Nutritional supplement allergy, Obstructive airways disorder, Occupational asthma, Occupational dermatitis, Ocular hyperaemia, Oculomucocutaneous syndrome, Oculorespiratory syndrome, Oedema, Oedema blister, Oedema genital, Oedema mouth, Oedema mucosal, Oedema neonatal, Oedema peripheral, Oral allergy syndrome, Oral mucosal exfoliation, Orbital oedema, Orbital swelling, Oropharyngeal blistering, Oropharyngeal oedema, Oropharyngeal spasm, Oropharyngeal swelling, Palatal oedema, Palatal swelling, Palisaded neutrophilic granulomatous dermatitis, Palpable purpura, Panniculitis, Pathergy reaction, Penile dermatitis, Penile exfoliation, Penile oedema, Penile rash, Penile swelling, Perineal rash, Perinephric oedema, Perioral dermatitis, Periorbital oedema, Periorbital swelling, Peripheral oedema neonatal, Peripheral swelling, Perivascular dermatitis, Pharyngeal oedema, Pharyngeal swelling, Photosensitivity reaction, Pneumonitis, Polymers allergy, Post procedural hypotension, Procedural shock, Prurigo, Pruritus, Pruritus allergic, Pulmonary eosinophilia, Puncture site rash, Radioallergosorbent test positive, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash maculovesicular, Rash morbilliform, Rash neonatal, Rash papular, Rash papulosquamous, Rash pruritic, Rash pustular, Rash rubelliform, Rash scarlatiniform, Rash vesicular, Reaction to azo-dyes, Reaction to colouring, Reaction to excipient, Reaction to flavouring, Reaction to food additive, Reaction to preservatives, Reaction to sweetener, Reactive airways dysfunction syndrome, Red man syndrome, Respiratory arrest, Respiratory distress, Respiratory failure, Respiratory tract oedema, Restlessness, Reversible airways obstruction, Rhinitis allergic, Rhinitis perennial, SJS-TEN overlap, Scleral oedema, Scleritis allergic, Scrotal dermatitis, Scrotal exfoliation, Scrotal oedema Scrotal swelling, Seasonal allergy, Sensation of foreign body, Septal panniculitis, Serum sickness, Serum sickness-like reaction, Shock, Shock symptom, Sinus tachycardia Skin erosion, Skin exfoliation, Skin necrosis, Skin oedema, Skin reaction, Skin swelling, Skin test positive, Sneezing, Soft tissue swelling, Solar urticarial, Solvent sensitivity, Status asthmaticus, Stevens-Johnson syndrome, Stoma site hypersensitivity Stoma site rash, Stomatitis, Streptokinase antibody increased, Stridor, Suffocation feeling Sunscreen sensitivity, Swelling, Swelling face, Swelling of eyelid, Swollen tongue, Symmetrical drug-related intertriginous and flexural exanthema, Tachycardia, Tachypnoea, Tattoo associated skin reaction, Throat tightness, Tongue exfoliation, Tongue oedema, Toxic epidermal necrolysis, Toxic skin eruption, Tracheal obstruction, Tracheal oedema, Tracheostomy, Transplantation associated food allergy, Type I hypersensitivity, Type II hypersensitivity, Type III immune complex mediated reaction, Type IV hypersensitivity reaction, Upper airway obstruction, Urticaria, Urticaria cholinergic, Urticaria chronic, Urticaria contact, Urticaria papular, Urticaria physical, Urticaria pigmentosa. Urticaria vesiculosa, Urticarial dermatitis, Urticarial vasculitis, Vaccination site dermatitis, Vaccination site eczema, Vaccination site exfoliation, Vaccination site hypersensitivity, Vaccination site photosensitivity reaction, Vaccination site rash, Vaccination site recall reaction, Vaccination site urticarial, Vaccination site vasculitis, Vaccination site vesicles, Vaccine associated enhanced disease, Vaccine associated enhanced respiratory disease, Vaginal oedema, Vaginal ulceration, Vascular access site dermatitis, Vascular access site eczema, Vasculitic rash, Vernal keratoconjunctivitis, Vessel puncture site rash, Vessel puncture site vesicles, Visceral oedema, Vomiting, Vulval eczema, Vulval oedema, Vulval ulceration, Vulvovaginal

exfoliation, Vulvovaginal rash, Vulvovaginal swelling, Vulvovaginal ulceration, Vulvovaginitis allergic, Wheezing.

The most clinically relevant hypersensitivity reactions occurred during or immediately following drug administration. Therefore, for post-marketing surveillance the following AEs will be used to monitor for these events.

AEs coded to a PT belonging to drug hypersensitivity, hypersensitivity, type I hypersensitivity, type II hypersensitivity, type IV hypersensitivity reaction, documented hypersensitivity to administered product or infusion related reaction are considered to be AEs possibly related to drug hypersensitivity reactions (MedDRA Version 26.1). Hypersensitivity reaction is an LLT that codes to the PT of hypersensitivity.

The MedDRA PTs that will be used for post-marketing surveillance are listed in **Annex 7**.

SVII.3.1.3 Important identified risk: clinical response characterised by loss of efficacy associated with anti-PEG antibodies

Frequency with 95% CI

Clinical trials:

At the time of this RMP, four pivotal studies (SNs 13401, 13024, 15912, 21824 [Part A], including the extension parts of SNs 13024 and 15912), and one phase 4 interventional study (SN 19764) have been completed. The AE frequencies are derived from pooled data of the above-mentioned studies.

Broad search criteria identify any potential case of loss of efficacy (LoE) and positive anti-drug antibody, and subsequently, cases where a final assessment of confirmed LoE related to anti-PEG antibodies are identified. An overview of the numbers of patients with any anti-drug antibodies who also had documented or potential loss of efficacy in studies of Jivi is provided in Table SVII-14 . These data are: Positive anti-drug antibody (anti-PEG, anti-PEG IgM, and BAY 94 NAB) and at least 1 TEAE of the following PTs ‘Drug ineffective’, ‘Drug-specific antibody present’, ‘Anti FVIII antibody positive’; Positive anti-drug antibody (anti-PEG, anti-PEG IgM, and BAY 94 NAB) and recovery <1 kg/dL at any time; Positive anti-drug antibody (anti-PEG, anti-PEG IgM, and BAY 94 NAB) and bleeding event ([SMQ ‘Haemorrhages’] from bleeding data or AEs) at the time of positive anti-drug antibody ± two weeks.

An additional search criterion “positive anti-drug antibody (anti-PEG, anti-PEG IgM, and BAY 94 NAB) and recovery <0.5 kg/dL at any time” was added to take into account the lower FVIII recovery observed in children without LODE /anti-drug antibodies (ADA) in the recently completed Part A of Alfa-PROTECT study (SN 21824). In 8/32 children in this study, single low recovery results were observed with values <1 kg/dL in the absence of anti-PEG antibodies. In two cases, the recovery was <0.5 without anti-PEG antibodies and without signs of LoE (lowest value 0.11 kg/dL). In all cases, these results have been observed only in single blood samples.

Therefore, the definition of LODE (defined as ≥1 times Factor VIII recovery <1 kg/dL) is not applicable for children and even a recovery <0.5 kg/dL is conservative as the observed recovery in the presence of neutralizing high titer anti-PEG antibodies in confirmed LODE cases is usually < 0.1 kg/dL.

Bleeding events are not a specific symptom of LoE, because it may be related to an insufficient dosing, especially when using extended intervals for prophylaxis.

Table SVII-14 : Patients with potential LODE and anti-drug antibodies in pooled analysis of Jivi SNs. 13401, 13024 part A including extension part (excluding subjects enrolled for Part B only), SN 15912 (main part and part 2) and extension, SN 21824 part A and SN 19764

Patients with any such event, n (%)	Age ≥7 years (N = 240)	Age <7 years (N = 48)	Total (N = 288)
Any anti-drug antibody and possible LODE	14 (5.8)	12 (25.0)	26 (9.0)
Possible LODE defined as TEAE of "drug ineffective", "drug-specific antibody present" or "anti-Factor VIII antibody positive"	1 (0.4)	7 (14.6)	8 (2.8)
LODE defined as ≥1 times Factor VIII recovery <1 kg/dL	6 (2.5)	7 (14.6)	13 (4.5)
LODE defined as ≥1 times Factor VIII recovery <0.5 kg/dL	2 (0.8)	3 (6.3)	5 (1.7%)
Any anti-drug antibody and any associated bleeding event within ± 2 weeks	10 (4.2)	5 (10.4)	15 (5.2)

IgM: Immunoglobulin M; LODE: Loss of Drug Effect; n: Number of Patients; N: Total number of patients in the population; PEG: Polyethylene Glycol; kg: Kilogram; dL: Deciliter
Bleeding event: Spontaneous bleeds reported in diaries (after start of study treatment) and all bleeds reported as treatment emergent adverse events are considered. SMQ "Hemorrhage terms (excl laboratory terms)" is used to identify bleeds reported as adverse events; SN: Study Number; TEAE: Treatment-Emergent Adverse Event, <: Less than; ≥: Greater than or equal to; %: Percent.

Of these 26 patients identified with the broad search criteria, there were 12 cases of perceived or confirmed loss of efficacy, 11 of which associated with anti-PEG antibodies which were neutralizing for Jivi activity. The majority of these 11 patients (10/11 patients) were aged <6 years (all from SN 15912) and one of these 11 patients was [redacted] years of age (SN 21824).Among those 11 patients: eight with loss of efficacy defined as a TEAE of "drug ineffective", "drug-specific antibody present" or "anti-Factor VIII antibody positive" and two with hypersensitivity being reported as the AE but with evidence of LODE [clinically or by low FVIII recovery]). One patient (a [redacted]-year-old [redacted] male) with low-titer anti-PEG IgM at baseline, prior to treatment and normal recovery at first infusion had LODE based on clinical assessment (bruising and inconclusive FVIII results, no ADA two weeks after start of treatment) and had no relevant TEAEs (withdrawn from the study on parents' decision after six ED due to a perceived lower efficacy compared to previous drug). One patient (a [redacted]-year-old, [redacted] male), also experienced contusion not responsive to study drug, but did not have serious AEs reported. This patient did not have anti-PEG antibodies or neutralizing antibodies (so not depicted in the above table) but did have FVIII recovery <1 kg/dL. In summary, the true LODE cases presented as very low FVIII recovery level (<0.1 kg/dL) and/or bleeding events that could not be controlled with Jivi administration and

the patients were withdrawn from the study. Most of the confirmed loss of efficacy (LoE) cases were associated with high titer anti-PEG antibodies (1:16 or higher).

In none of the remaining patients identified by screening, associated bleedings were assessed as loss of efficacy; most occurred in patients receiving the once weekly treatment regimen. All of the patients continued in the study without signs of loss of efficacy.

None of these 26 patients identified with the broad search criteria developed a FVIII inhibitor.

The clinical implications of the presence of anti-PEG IgM antibodies prior to exposure to Jivi is very different from the development of anti-PEG IgM antibodies in response to Jivi administration. The Table SVII-14 included patients with antibodies prior to Jivi together with patients who developed anti-PEG antibodies following drug exposure.

SN 19764: No relevant cases have been reported.

SN 21824: One case of LoE (included in the summary above) has been reported in an [redacted]-year-old study participant who experienced LoE (low FVIII recovery of 0.06 kg/dL) due to transient high-titer IgM anti-PEG antibodies, which developed after the second ED. Jivi treatment was temporarily discontinued. The study participant resumed treatment with Jivi after two months without any further immune response to PEG.

Low titer (highest titer 1:4) *de novo* anti-PEG IgM antibodies were detected in three further participants within the first four EDs, leading to mildly decreased recovery in two of these subjects (the lowest recorded recovery was 0.8 kg/dL) that was not associated with spontaneous bleeding events.

In addition, two patients had pre-existing low titer IgM anti-PEG antibodies that were not associated with signs/symptoms or LoE and disappeared before or during the treatment.

Pooled data of patients from age group 7 to <12 years of age (N = 59): Based on the pooled data of 59 patients from age group 7 to <12 years of age (including SN 21824 and SN 15912) with only one case of LoE associated with anti-PEG antibodies observed, the estimated true incidence of an LoE during first four EDs in this age group is <5% (posterior probability 92.2%; the median of the posterior probability distribution is 1.59%).

Overall conclusion:

In PTP children <7 years of age the immune response associated with anti-PEG antibodies (both LODE and hypersensitivity reactions) was more pronounced, than in PTPs ≥7 years: significantly higher anti-PEG IgM antibody titer were recorded, the incidence of LODE cases was also higher (approximately 20% in children <7 years of age *vs.* <5% in children 7-<12 years and zero cases in PTPs of 12 years of age and older), and hypersensitivity events related to Jivi were both more frequent and more severe/serious in patients <7 years of age.

Post-marketing surveillance

Lack of drug effect associated with anti-PEG antibodies has only been reported within ED 2-4. The reported incidence of lack of drug effect and/or hypersensitivity is consistent with that observed in the clinical trials.

Literature data regarding other PEG-linked biologicals show that anti-PEG antibodies can occur. PEG by itself is not considered antigenic unless coupled to a protein or given with adjuvants that may strongly facilitate an immune response. In contrast to this general assumption, anti-PEG antibodies have been found in samples obtained from healthy donors, possibly because of exposure to PEG-based cosmetics, pharmaceuticals, and food preparations (233-235).

To date, only two highly immunogenic non-human proteins linked to PEG have been found to induce formation of anti-PEG antibodies: these are PEG-asparaginase and PEG-uricase (236, 237). PEG-uricase induced the formation of IgG antibodies, mostly IgG2 specific for PEG, in 9 of 24 patients in a phase 1 clinical study (237). PEG-asparaginase and PEG-uricase showed a trend towards a more rapid clearance (236, 237). In fact, Ganson *et al.* observed that anti-PEG antibodies did not inhibit enzyme activity, but caused a more rapid degradation of the protein (238). Interestingly, in a PEG-asparaginase trial fewer patients developed antibodies to the PEGylated protein than to the natural enzyme (239). PEGylation of asparaginase appeared to reduce immunogenicity by more than half, with high titre antibodies occurring in 26% of patients receiving native *E. coli* asparaginase and 2% of those receiving PEG-asparaginase. It was concluded that the PEGylation of asparaginase reduces its immunogenicity and prolongs its duration of action. However, antibodies developed against the natural protein can still recognise domains of the PEGylated protein.
Zalewska-Szewczyk *et al.* studied the cross-reactivity of different asparaginase preparations (*E. coli*, *Erwinia* and PEG-asparaginase) and demonstrated a cross-reaction to PEG-asparaginase in serum from patients with allergic reactions to *E. coli* asparaginase, even though the patients had never received PEG-asparaginase (240).

Garay and Labaune performed a review of the literature concerning immunogenicity of PEG alone or covalently attached to proteins. They concluded that anti-PEG antibodies (pre-existing or newly developed) may accelerate the clearance of PEGylated proteins and limit therapeutic efficacy and/or reduce tolerance to the PEGylated products used in the clinic (241).

Seriousness/outcomes

Anti-PEG antibodies (pre-existing or newly developed) appear to accelerate the clearance of PEGylated proteins thereby limiting therapeutic efficacy (241).

PEGylation appears to reduce immunogenicity of proteins, and hypersensitivity reactions seem rather to depend on the protein moiety (128), i.e., rFVIII in the case of Jivi.

In the clinical development program for Jivi, pre-existing anti-PEG antibodies were not predictive of LoE. Similarly, in paediatric patients with severe haemophilia A treated with glycoPEGylated rFVIII (turoctocog alpha pegol, N8-GP) pre-existing anti-PEG antibodies were not predictive of an immune response and disappeared after start of treatment.
Pre-existing anti-PEG antibodies could result in a minor reduction of recovery in some of the cases (242).

The clinical impact of *de novo* anti-PEG antibodies observed with Jivi was dependent on the antibody titer: true LODE was associated with high titer of the anti-PEG IgM antibodies

(predominantly in children < 6 years of age), whilst low titer anti-PEG IgM antibodies were associated only with mildly reduced recovery. Similarly, in a study with turoctocog alfa pegol in PTP patients <12 years of age one patient had low titer de novo anti-PEG antibodies, which had no clinical relevance (influence on PK) (242).

The *de novo* anti-PEG antibodies observed with Jivi were of the IgM isotype. No class switching was observed. The anti-PEG IgM antibodies were transient, i.e., titers declined over time becoming negative weeks to months after discontinuation. All patients with LODE, which was observed predominantly in patients <6 years of age, resolved their loss of drug effect upon switching to their previous Factor VIII replacement therapy. In one case, the patient resumed treatment with Jivi two months after the treatment discontinuation without immune response upon the re-challenge.

For the 12 cases of perceived or confirmed loss of efficacy, five were serious, three were non-serious, two were serious hypersensitivity with evidence of LODE but no LoE reported as AE, one was non-serious without anti-PEG antibodies and in one case, no AEs were reported (suspected LoE). All the serious LODE cases were reported in children <6 years of age.

In five of the eight patients with loss of efficacy (includes patient 15912[redacted] who experienced hypersensitivity as the primary event prior to obtaining laboratory evidence of loss of efficacy) defined as a TEAE of 'drug ineffective', 'drug-specific antibody present' or 'anti-FVIII antibody positive', the event was classified as serious. All of them were <6 years of age. Four of these 5 patients with loss of efficacy had anti-PEG antibodies; in 3 cases the antibodies subsequently became undetectable and in the 4th case the titre of anti-PEG antibodies had decreased at the final visit. Details of these patients are presented below.

- Patient 15912[redacted], a [redacted]-year-old [redacted] male, was reported as flushed and weak after the 3rd and 4th exposure to study drug. The 5th infusion was administered under physician supervision, during which the patient was observed to become hypotensive (60/40 mmHg) with oxygen desaturation (80%). The patient was put in a supine position, treated with 5 L oxygen and recovered over 15-20 minutes. Central and local testing collected 20 minutes after the infusion of study drug (26 IU/kg) demonstrated a FVIII level of <1%. Drug hypersensitivity of moderate intensity considered to be related to the study drug was reported as a serious AE and study drug was withdrawn. Suspected inhibitor of moderate intensity was also reported as a serious AE. Testing 2 days after the event and 2 and 8 weeks later ruled out FVIII inhibitor. The patient resumed his prior treatment with another FVIII product and on follow-up was reported to be doing well without sequelae. Antibodies to Jivi and PEG were negative at baseline, but titres became positive two weeks after study drug was withdrawn. Approximately eight weeks after last study drug exposure, antibodies to Jivi and to PEG were undetectable. Subsequent testing was notable for detectable anti-PEG IgM prior to first drug exposure. FVIII inhibitor antibodies remained negative (< 0.2 BU) at all measurements.
- Patient 15912[redacted], a [redacted]-year-old [redacted] male, complained briefly of a 'dry cough' after his third infusion of study drug, but no respiratory distress or

abnormalities in vital signs were observed. Later on, the same day, the patient had a trauma in the left calf and on the following day the patient developed a haematoma in the left calf and in the right scrotum. A dose of study drug was applied to treat the bleed (4th infusion of study drug) with poor response and an additional infusion of study drug was applied the next morning (5th infusion of study drug). The investigator felt that there was no improvement in the haematomas. An infusion of commercial FVIII (Helixate) was performed on the same day and it was later reported that there was an improvement in the bleeds. Loss of efficacy was reported as a serious AE ***(PT: drug ineffective)*** and was considered related to study drug. The patient had positive results for antibodies to PEG, PEG IgM and Jivi around the time of the event. The titres of the antibodies decreased at the final visit, approximately one month later. FVIII inhibitor was negative at all measurements. The patient responded to his previous FVIII replacement therapy.

- Patient 15912[redacted], a [redacted]-year-old [redacted] male, had haematomas on both legs reported 7 days after start of study drug (2 days after the 2nd ED). No treatment was applied to these haematomas. Two days later a regular prophylaxis infusion was administered and later in the same day a spontaneous haematoma in the left knee was reported. No additional FVIII was applied to treat this haematoma. On the next day, a third haematoma (spontaneous haematoma in right instep) was reported. On the following day, the patient went to the site when central testing collected 30 minutes after the infusion of study drug (55 IU/kg) demonstrated a FVIII level of 5%.
  The patient discontinued study drug and returned to the previous product due to perceived loss of efficacy of the study drug. Antibodies to Jivi and PEG were negative prior to exposure to study drug. FVIII inhibitor antibodies remained negative (<0.2 BU) at all measurements. Occurrence of BAY antibodies and PEG antibodies were reported as serious AEs by the investigator and considered to be related to the study drug. The patient responded to his previous FVIII replacement therapy.
- Patient 15912[redacted], a [redacted]-year-old [redacted] male, had bruising reported by the parents after two days from start of study drug (1 ED). On the next day the parent reported swelling of the right thigh and the patient received 1 dose of study drug as treatment for spontaneous bleed. Two days later the patient received his scheduled prophylactic infusion and on the next day left ankle bleeding was reported, however no further study drug was administered to treat the event. Study drug was withdrawn due to perceived loss of efficacy of the study drug and the patient was switched back to his prior FVIII product. The subject had reduced FVIII measurement (38.7%) following first exposure to Jivi (55 IU/Kg) reported by the central laboratory.
  No additional testing for recovery was obtained. Suspicion of Jivi antibodies and PEG antibodies were reported by the investigator as serious AEs and considered to be related to the study drug. Neutralising antibodies to Jivi were detected following drug administration. FVIII inhibitor was negative. The patient was later reported to be doing well on his prior treatment regimen.
- Patient 15912[redacted], a [redacted]-year-old [redacted]male, had subcutaneous haematomas reported starting 3 days after start of study drug (2 ED). The patient continued

receiving his regular prophylactic infusions twice a week and 10 days later the parent reported, in addition to the subcutaneous haematomas, swelling in the left ankle which was treated with an infusion of study drug. On the following day the patient went to the hospital and received a follow-up infusion of study drug. Central testing collected 30 minutes after the infusion of study drug (66.7 IU/kg) demonstrated a FVIII level of 8%. Study drug was withdrawn 4 days later due to perceived loss of efficacy of study drug and the patient was switched back to his prior FVIII product. Antibodies to Jivi and PEG were positive following drug administration and became negative with ongoing follow-up. FVIII inhibitor antibodies remained negative (<0.2 BU) at all measurements. "Anti-PEG antibodies" was reported by the investigator as a serious AE and was considered to be related to the study drug. The patient responded to his previous FVIII replacement therapy.

The three remaining patients had a non-serious TEAE of 'drug-ineffective', 'drug-specific antibody present' or 'anti-Factor VIII antibody positive' and anti-PEG antibodies (transient in all three cases); these patients are described below.

- Patient 15912[redacted] ([redacted]-year-old, [redacted]) experienced bruising after the second dose of study drug, followed by shivering during the 3rd infusion of study drug (which had also been observed previously during infusion of commercial FVIII product). Loss of efficacy of the study drug (***PT: drug ineffective***) was reported as an AE of special interest and the patient withdrew from the study due to this AE after 6 EDs. Antibodies to Jivi and PEG were detected after drug administration.
  On follow-up more than three months following the last Jivi application, all anti-drug antibody measurements were negative. The patient responded to his previous FVIII replacement therapy.
- Patient 15912[redacted] ([redacted]-year-old, [redacted]) had positive neutralising antibodies to Jivi at baseline and at subsequent visits. Loss of efficacy of the study drug was reported as an AE of special interest (***PT: drug ineffective***) and the patient was withdrawn from the study due to this AE after 3 EDs. All subsequent anti-drug antibody measurements were negative. The patient responded to his previous FVIII replacement therapy.
- Patient 21824[redacted] ([redacted]-year-old, [redacted]) experienced LoE after two ED (very low recovery 0.06 kg/dL at ED3) in the presence of high titer IgM anti-PEG antibodies (1:64). The participant discontinued Jivi and went back to his prior FVIII medication, until the antibodies disappeared. Participant re-started treatment two months later after disappearance of anti-PEG antibodies. He did not present any immune reaction, there was no class switch to IgG antibodies, the patient had a normal recovery and continued treatment in the extension study.

For 4 patients, loss of efficacy was not directly reported but assessed *via* post-infusion FVIII levels/recovery. Three patients discontinued treatment due to hypersensitivity reported as a SAE and had positive anti-PEG antibodies results during the event. The possible seriousness and outcome of hypersensitivity reactions to FVIII were previously discussed. In addition,

one patient experienced contusion not responsive to study drug and reported as non-serious AE. This patient did not have anti-PEG antibodies or neutralising antibodies.

Severity and nature of risk

Table SVII-15 presents the severity of anti-PEG antibody formation (titre) and associated loss of efficacy that occurred in Jivi clinical studies.

Table SVII-15: Severity of anti-PEG antibodies and associated LoE in Jivi clinical studies

Study/patient Number Age	Maximum titre Anti-PEG	 Anti-PEG IgM	Reported PTs related to antibodies and LoE	Maximum intensity of reported PTs related to antibodies and LoE	Maximum intensity of bleeding events related to antibodies and LoE[a]	Lowest FVIII recovery (kg/dL) Lowest FVIII post-infusion level[e]
Cases considered as true LoE						
15912[redacted]-year-old	16	256	Anti FVIII antibody positive[b]	Moderate	N/A	0.0[e]
15912[redacted]-year-old	64	128	Drug ineffective	Moderate	NR	0.0[e]
15912[redacted]-year-old	8	16	Drug-specific antibody present	Severe	Moderate	<0.1[e]
15912[redacted]-year-old	neg[c]	neg[c]	Drug-specific antibody present	Severe	N/A	0.684
15912[redacted]-year-old	16	128	Drug-specific antibody present	Severe	Moderate	<0.2 (FVIII post infusion 6.3%)2.45
15912[redacted]-year-old	64	128	Drug ineffective	Moderate	N/A	0.0[e]
15912[redacted]-year-old	neg	1	Drug ineffective	Mild	N/A	0.013
15912[redacted]-year-old	4	16	N/A[b]	N/A	Moderate	0.932
15912[redacted]-year-old	0	4	N/A	N/A	N/A	1.75
15912[redacted]-year-old	neg[d]	neg[d]	N/A	N/A	Mild	0.30

Table SVII-15: Severity of anti-PEG antibodies and associated LoE in Jivi clinical studies

Study/patient Number Age	Maximum titre Anti-PEG	 Anti-PEG IgM	Reported PTs related to antibodies and LoE	Maximum intensity of reported PTs related to antibodies and LoE	Maximum intensity of bleeding events related to antibodies and LoE[a]	Lowest FVIII recovery (kg/dL) Lowest FVIII post-infusion level[e]
15912[redacted] [redacted]-year-old	32	128	N/A	N/A	N/A	0[e]
21824[redacted] [redacted]-year-old	64	64	Drug ineffective	Moderate	N/A	0.06

[a] Associated bleeding events within ± 2 weeks of positive anti-drug antibody.
[b] These patients also had a TEAE of “drug hypersensitivity” or “hypersensitivity”.
[c] This patient had neutralizing antibodies and had “suspicion of PEG antibody” reported but was not positive for anti-PEG or anti-PEG IgM antibodies.
[d] This patient did not have anti-PEG antibodies or neutralizing antibodies but did have FVIII recovery <1 kg/dL.
[e] For the following patients recovery was not calculated but low or undetectable FVIII levels post-infusion were measured during the visits corresponding the relevant TEAEs:
[redacted] (FVIII level < LLOQ post-infusion), [redacted] (FVIII level <LLOQ), 240010001 (FVIII <LLOQ).
[redacted] (FVIII level <LLOQ), [redacted] (FVIII <LLOQ), [redacted] (FVIII level <LLOQ)
[redacted] (FVIII level post-infusion 5.2 IU/dL)
[redacted] (FVIII level post-infusion 6.3343 IU/dL)
[f] perceived LoE by parents, no bleed
IgM: Immunoglobulin M; LODE: Loss of Drug Effect; LLOQ: Lower limit of quantification; n: Number of patients; N: Total number of patients in the population; N/A: Not Applicable; ND: Not Done; neg: Negative; NR: Not Reported; PEG: Polyethylene Glycol.

The development of antibodies to Jivi or to the PEG moiety occurs within the first 4 EDs. The key risk is in not recognising that FVIII levels are reduced due to accelerated drug clearance. This could result in unanticipated bleeding events, a lack of response to a bleeding event, or unexpected bleeding despite prophylaxis during surgery. The severity of the event is related to the nature of the bleed. Understanding the timing of this risk in relation to the initiation of Jivi provides for implementation of effective risk mitigation strategies (**Section SVII.3.1.3, Preventability**).

Post-marketing surveillance

The majority of adverse reactions received from the post-marketing surveillance were non serious.

The antibodies are specific to Jivi and there is no evidence that these antibodies will interfere with other FVIII products.

Background incidence/prevalence

The frequency of pre-existing anti-PEG antibodies in patients with no previous exposure to PEG-linked biologicals is unclear: literature reports present different frequency figures, with one early publication reporting frequencies of 0.2% in healthy donors and 3.3% in untreated, allergic patients (233), compared with reported frequencies of 22–25% in healthy donors or up to 72% in the general population in more recent publications (234, 235, 243).

A study of Armstrong *et al.* documented appearance of anti-PEG antibodies in patients with acute lymphoblastic leukaemia who had documented prior exposure to PEG-asparaginase (236). Eight of the 16 patients studied (50%) had undetectable asparaginase activity and were positive for anti-PEG.

Antibodies to PEG were analysed in patients with various allergies employing passive haemagglutination. During hyposensitisation with monomethoxy PEG (mPEG)-modified ragweed extract and honeybee venom, respectively, the patients showed an anti-PEG antibody response. Fifty percent of the patients developed anti-PEG antibodies directly after the first treatment course; after two years of treatment the percentage of patients declined to 28.5%. The anti-PEG antibodies were predominantly of the IgM isotype, and the weak IgM response found in treated patients was considered to be of no clinical significance (233).

Ganson *et al.* did not see anti-PEG antibody formation in patients treated with PEG-adenosine deaminase, even in those treated for longer than a decade (unpublished results) (238). More recently, Hamad *et al.* (244) reported that extremely high concentrations of near-monodisperse endotoxin-free PEGs can generate complement activation products in human serum on a time scale of minutes, but stated that the pathway involved was not antibodies activating complement. Tillmann *et al.* found a high frequency of PEG antibodies in patients with hepatitis C on treatment with PEG-IFN (245). However, these PEG antibodies did not lead to impaired response to treatment.

Risk groups or risk factors

Age is the primary risk factor for the generation of anti-PEG IgM antibodies. The incidence was significantly higher in patients 6 years of age and younger. The increased risk of immune response to PEG with hypersensitivity reaction and/or LoE was limited to the first 4 exposures with no additional cases observed at a later time point.

Review of additional medical history in the Study 15912 (PROTECT Kids and Alfa PROTECT) did not clearly identify any clinical risk factors for occurrence of AEs. Additionally, presence or absence of anti-PEG antibody prior first administration shows low predictive value.

Potential mechanisms

Anti-PEG antibodies have been associated with a more rapid drug clearance for PEG-asparaginase and PEG-uricase (236, 237). The accelerated clearance of Jivi in the presence of anti-PEG antibodies as demonstrated by the low FVIII recovery appears to be responsible for the loss of efficacy observed clinically.

As discussed in **Section SVII.3.1.2 (Preventability)**, the production of exclusively IgM antibodies in response to a stimulus can be produced by either the marginal zone B cells or the B-1b cell population. The incidence of both hypersensitivity reactions and high titres of anti-PEG IgM antibodies leading to loss of efficacy occur primarily in young children <6 years of age. This suggests that the B-1b cell population which develops in utero is more likely to be responsible for the generation of the anti-PEG antibodies in response to Jivi administration. This is a T-cell independent immune response without a long-term memory. When Jivi is discontinued, the anti-PEG IgM titers decrease becoming undetectable over time. No class switching has been observed. Baumgarth (246) summarizes the immunology involved the development of these IgM antibodies.

The B-1b cells undergo mutations in their immunoglobulin genes that approximate the adult before 6-7 years of age (232). These changes in the immune system may be responsible for the low incidence of anti-PEG IgM generation following the administration of Jivi in adults. In the clinical trial program with Jivi the vast majority of LoE cases associated with high titer anti-PEG IgM antibodies was observed in children 2-5 years of age. In one child [redacted] years of age, the immune response to PEG occurred after the second infusion (232).

Preventability

The two known risks for the development of anti-drug antibodies and associated loss of efficacy are age <6 years and the first 4 administrations.

The risk can be minimized by restricting treatment to patients >6 years of age.
Since mutations in the B-1b cells (most likely cell population to be responsible for antibody production following drug exposure) are thought to approximate the adult phenotype around age 6-7 years a conservative approach was adopted for the initial approval to restrict use to age ≥12 years.

Based on the pooled data of 59 patients from the age group 7 to <12 years of age (SN 21824 and SN 15912), where only one case of LoE associated with transient anti-PEG antibodies occurred within the first four EDs (i.e., true incidence <5%, with posterior probability of 92.2%), the proposed indication extension is to include patients age ≥7 years.

The timing of antibody development enables risk mitigation by focusing on signs/symptoms that could represent a bleeding event during the first few drug administrations. It also enables identification prior to any bleeding event by obtaining a FVIII recovery following the 3rd or 4th administration when an accelerated clearance secondary to antibody formation would occur. This FVIII recovery can also be used to verify or modify the dosing regimen as appropriate.

According to the Development core safety information (DCSI), Jivi should be used with caution in patients with a known hypersensitivity to PEG.

In the Jivi clinical trial programme, the vast majority cases of true loss of efficacy associated with anti-drug or anti-PEG antibodies occurred in patients aged <6 years, and only one case was reported in an [redacted]-year-old patient, and all patients were able to switch back to their

previously effective FVIII therapy. Use of Jivi in patients aged <7 years is not included in the proposed label.

Impact on individual patient

The impact on an individual patient who experiences loss of efficacy may involve a bleeding event. All patients experiencing loss of efficacy secondary to the development of anti-PEG and/or neutralising antibodies to Jivi were switched to their previous FVIII replacement product with which satisfactory efficacy occurred.

There is no long-standing immune memory to Jivi. Once the patient has effectively switched to another FVIII treatment, there is no further impact.

The impact on quality of life of anti-PEG antibodies that might develop during Jivi treatment in patients with haemophilia is not fully known yet. No cross-reactivity of anti-PEG IgM antibodies with other unmodified FVIII products was observed and no switch to IgG class was observed, suggesting no long-term memory of an immune response to PEG. In addition, all patients could be treated with their previous FVIII product; and therefore, the impact is expected to be limited.

Due to the transient nature of the immune response associated with anti-PEG IgM antibodies, and absence of a switch to IgG and, consequently, of long-term memory of this immune response, a re-start of Jivi can be considered upon disappearance of the antibodies (estimated time 4-6 weeks after Jivi discontinuation). Factor VIII level should be checked upon re-start of Jivi.

Potential public health impact of safety concern

In case of lack of efficacy associated with anti-PEG antibodies, it may be necessary to discontinue treatment with Jivi, and the patient has to explore other options. Anti-PEG antibodies associated with loss of efficacy are generally transient, and patients were able to switch back to their previous FVIII therapy. Since there are many therapeutic options for patients with Haemophilia A, there is no public health concern.

Evidence source

Refer to **Annex 7**.

MedDRA terms

For the analyses presented in this section: a search was conducted for the following PTs: “drug ineffective”, “drug-specific antibody present’ and ‘anti-FVIII antibody positive”. Additional relevant cases were identified by manual case review. Positive anti-drug antibody (anti-PEG, anti-PEG IgM, and Jivi neutralising antibody were considered) and recovery <1 kg/dL at any time; anti-drug antibody (anti-PEG, anti-PEG IgM, and Jivi neutralising antibody were considered) and bleeding event (from bleeding data or AEs) at the time of positive anti-drug antibody ± two weeks. The SMQ ‘Haemorrhages’.

For post-marketing surveillance, MedDRA search terms for loss of drug efficacy due to anti-drug antibodies will include the following PTs: drug ineffective, drug-specific antibody

present anti-FVIII antibody positive, and drug effect decreased. Additional cases may be identified during assessor review of bleeding events with low FVIII recovery.

The MedDRA PTs included to be used in post-marketing surveillance are listed in **Annex 7.2**.

SVII.3.1.4 Important potential risk: Thromboembolic events

Normalization of FVIII levels in patients with existing cardiovascular risk factors have the potential to result in thromboembolic events.

The SmPC includes the following information for cardiovascular events:

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

There were no thromboembolic events observed during the clinical program for Jivi.

Post-marketing surveillance

No distinct pattern can be discerned with the limited number of cases reported to date.

The information received from the post-marketing experience did not reveal any new safety findings which would necessitate additional actions.

SVII.3.1.5 Important potential risk: Off-label use

Immunogenicity related to increasing titres of anti- polyethylene glycol (PEG) immunoglobulin M (IgM) antibodies has been reported in children <6 years. Jivi is not indicated for individuals age <7 years, which will reduce the risk of immunogenicity related reactions.

Post-marketing surveillance

To the DLP of this report there was a small number ICSRs of Jivi use in children< 7 years of age received in the company safety database.

No safety concerns were identified on review of the data received with these cases.

SVII.3.1.6 Important potential risk: Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs

This risk was included in the Initial EU-RMP (Procedure EMEA/H/C/004054/IAIN/0013) based on non-clinical finding (vacuolation in the choroid plexus of the brain and other tissues/organs) with other PEGylated compounds. No vacuolation was observed in non-clinical studies with Jivi.

Based on the available evidence to the DLP of this RMP, including

- recently published non-clinical data for other PEGylated products,
- clinical experience in patients treated with Jivi for ≥5 years in the extension parts of the pivotal studies PROTECT-VIII and PROTECT-Kids (N = 75, including 39 patients <12 years of age) and

- during >6 years of post-marketing experience [including data from ongoing and completed PASS studies], predominantly in the approved population),

no data was identified suggestive of PEG accumulation and associated potential clinical consequences being a safety concern for patients treated Jivi.

The evidence is discussed in detail in the eCTD submitted as a part of Type II C.I.6 and in responses to RSI and AR for the Procedure: EMEA/H/C/004054/II/0034).

SVII.3.2 Presentation of the missing information

SVII.3.2.1 Missing information: Use in patients with severe hepatic impairment

Patients were excluded from pivotal studies and from the PMI study (SN 19764) to reduce the impact of co-morbidities on the homogeneity of the study population (liver disease is associated with abnormal haemostasis). Patients with abnormal hepatic function were included in interventional studies and post-marketing non-interventional studies of Kogenate Bayer/Kovaltry. No safety concerns were detected. The PEG moiety of Jivi is expected to be secreted in urine and to a lesser extent, in bile. At extremely high PEG doses after repeated administration, vacuolation of Kuffer cells and hepatocytes have been reported in non-clinical studies with other PEGylated products. Vacuolation was not observed in any of non-clinical studies with Jivi. Based on the findings from the 26 weeks chronic toxicology study with Jivi, clinically relevant accumulation of PEG in the liver in patients with severe hepatic impairment is not expected.

Clinical data from patients treated with Jivi for ≥5 years:

Based on clinical experience in patients treated with Jivi for ≥5 years in the extension parts of the pivotal studies PROTECT-VIII and PROTECT-Kids (N = 75, including 39 patients <12 years of age), no evidence of treatment-related worsening of liver function was identified on review of TEAEs or liver function parameters.

SVII.3.2.2 Missing information: Use in patients with renal insufficiency

Patients were excluded from pivotal studies and from the PMI study (SN 19764) to reduce the impact of co-morbidities on the homogeneity of the study population (kidney disease is associated with abnormal haemostasis). Patients with abnormal renal function were included in post-marketing non-interventional studies of Kogenate Bayer/Kovaltry. No safety concerns were detected. The PEG moiety of Jivi is expected to be secreted in urine. Plasma PEG levels will increase with worsening renal insufficiency. Modelling shows that 90% loss of renal clearance results in plasma PEG concentration of 1.0 mg/L. This is approximately five times lower than the steady state plasma concentration of PEG reported with Refixia (5.0 mg/L). The long-term preclinical toxicology study did not reveal any renal findings with Jivi.

Accumulation of PEG in patients with decreased renal function should not result in any clinical issues. Patients with end-stage renal disease represent complex patients with multiple morbidities for whom information on the use of FVIII replacement products is limited.

Clinical data from patients treated with Jivi for ≥5 years:

Based on clinical experience in patients treated with Jivi for ≥5 years in the extension parts of the pivotal studies PROTECT-VIII and PROTECT-Kids (N = 75, including 39 patients <12 years of age), no evidence of treatment-related worsening of renal function was identified on review of TEAEs, biomarkers of renal safety and relevant laboratory tests results.

SVII.3.2.3 Missing information: use in elderly patients >65 years of age

Patients with haemophilia in this age group are less common and often are unwilling to receive frequent prophylactic injections.

For participation in clinical trials, patients must be able to enter infusion data in electronic diaries. This may be challenging for the patients aged >65 years. There is limited experience in patients >65 years of age in the ongoing extension study 13024 and in SN 19764. No new safety concerns have been identified.

Clinical experience with Kogenate Bayer and Kovaltry and other FVIII products has not identified differences between the elderly and younger patients. In general, co-morbidities associated with ageing (such as CVD) are also challenges in the haemophilia population.

SVII.3.2.4 Missing information: safety profile in women including pregnancy and lactation

As an X-linked recessive disease, severe haemophilia is quite rare in women. The use of Jivi is expected to be similar in women as in men. There is limited data with severe haemophilia in pregnant women with any FVIII product. Jivi does not cross the placenta and is not expected to be secreted in breast milk.

Post-marketing surveillance

To the DLP of this EU RMP there was a small number (N = 13) ICSRs received from the post-marketing experience concerning women treated with Jivi for hemophilia A or "hereditary factor VIII deficiency" and further 10 cases with the indication not specified. In most of the cases the reported adverse events were typical signs of the underlying haemophilia (e.g., haemorrhage, haemarthrosis). No new safety concerns were identified.

PART II: Module SVIII - Summary of the safety concerns

Table SVIII-1: Summary of safety concerns

Important identified risks	• Development of FVIII inhibitors • Hypersensitivity reactions • Loss of efficacy associated with anti-PEG antibodies
Important potential risks	• Off-label use • Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs • Thromboembolic events
Missing information	• Use in patients with severe hepatic impairment • Use in patients with renal insufficiency • Use in elderly patients >65 years of age • Safety profile in women including pregnancy and lactation

PEG: Polyethylene Glycol; >: Greater than.

PART III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Similar to marketed products, medical products under development are subject to medical safety surveillance at Bayer AG. Routine PV will be conducted for Jivi as detailed in corresponding PV procedures. All these routine procedures are described in applicable Standard Operating Procedures.

Routine PV activities beyond ARs reporting and signal detection:

III.1.1 Specific adverse reaction follow-up questionnaires

Targeted follow-up questionnaire will be used for specific single cases received during the post-marketing period. The risks covered by the questionnaires, their titles and content are shown in Table Part III-1**. (See Annex 4)**

Table Part III-1: Relationship between risks and specific adverse reaction questionnaires

Risk	Questionnaire Title	Questionnaire Content
Hypersensitivity reactions	Questionnaire for Health Care Professionals concerning a potential hypersensitivity reported in association with Jivi	Additional information regarding the hypersensitivity event
Long-term potential effects of polyethylene glycol (PEG) accumulation in the choroid plexus of the brain and other tissues/organs	1. Follow-up questionnaire for renal impairment 2. Follow-up Questionnaire for neurocognitive disorders	1. Additional information pertinent to the evaluation of renal impairment 2. Additional information pertinent to the evaluation of cognitive dysfunction
Loss of drug effect associated with development of FVIII inhibitors	Questionnaire for Health Care Professionals concerning a potential loss of drug effect reported in association with Jivi	Additional information pertinent to the evaluation of loss of drug effect
Loss of efficacy associated with anti-PEG antibodies	Questionnaire for Health Care Professionals concerning a potential loss of efficacy reported in association with Jivi	Additional information pertinent to the evaluation of loss of efficacy

The objective will be to analyse reported cases to determine whether any patterns become obvious and to delineate the clinical factors that may be positively associated with the development of identified risks and missing information.

III.1.2 Other forms of routine pharmacovigilance activities

Not applicable

III.2 Additional pharmacovigilance activities

Category 1 – Post-authorisation safety study (Study 20904)

Study short name and title:

Observational study evaluating long-term safety of real-world treatment with Jivi (Damoctocog alfa pegol) in PTPs with Haemophilia A

Rationale and study objectives:

To fulfil the requirement of 50 subjects followed for at least 4 years to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs.

The key objectives are:

The primary objective of this study is to assess the long-term safety of prophylaxis with Jivi in patients with haemophilia A in the real-world setting through the collection and analysis of AEs of special interest including those potentially indicative of PEG accumulation (hypersensitivity reactions, loss of drug effect, renal impairment, neurocognitive disorders, and inhibitor development), AEs, SAEs, and ARs.

The secondary objective is to monitor the clinical effects of long-term exposure of prophylaxis Jivi in patients with haemophilia A, including assessments of kidney and liver function parameters, neurological function and patients' PEG plasma levels.

Study design:

Multicentre, multinational, open-label, prospective, non-interventional, cohort study.

Study population:

Previously treated patients ≥12 years with haemophilia A.

Milestones:

FPFV Q2/2021.

Study completion by Q2/2028, final study report by Q4/2028.

Category 3 - EUHASS registry (study 14149)

Study short name and title:

EUHASS registry (Study 14149)

Rationale and study objectives:

The EUHASS registry is an investigator-driven registry that is funded by the European Commission's Consumers, Health and Food Executive Agency (CHAFEA) in addition to Bayer and other manufacturers of FVIII concentrate products. EUHASS is a prospective

Haemophilia Safety Surveillance System for Europe. Participating centres have agreed to report all relevant AEs in their patients in a prospective manner. Events, that should be reported, are new inhibitors, infections, allergic reactions, thromboses, new malignancies, deaths, unexpected poor efficacy, and other AE possibly related to the FVIII. EUHASS will address the important identified risks of development of FVIII inhibitors and hypersensitivity, and missing information on potential long-term PEG-related ARs (through collection of safety data related to renal impairment and neuro-cognitive disorders).

The primary objectives are:

- to establish a PV programme to monitor the safety of treatments for patients with haemophilia.
- to develop and maintain a database of haemophilia centres in Europe.
- to establish a Rapid Alert System for immediate Europe-wide notification of professionals treating patients with haemophilia, in case of unexpected or serious AEs.

Study design:

EUHASS is a prospective Haemophilia Safety Surveillance System for Europe.

Study population:

Over 10,000 PWHA in multiple centres in Europe.

Milestones:

An update will be provided with each Periodic Benefit-Risk Evaluation Report (PBRER)/Periodic Safety Update Report (PSUR).

III.3 Summary table of additional pharmacovigilance activities

Table Part III-2: 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				
Prospective multinational non-interventional Post-Authorisation Safety Study (PASS) study 20904 HA-SAFE	To provide long-term safety data to investigate safety risks associated with Jivi use for prophylaxis in the real-world settings, including the potential effects of polyethylene glycol (PEG) accumulation in the choroid plexus of the brain and	Potential long-term PEG-related adverse reaction (ARs) Hypersensitivity reactions Loss of efficacy associated with anti-PEG antibodies Development of FVIII inhibitors	First Patient Visit Study completion Study Report	Q2 2021 Q2/2028 Q4/2028

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

Table Part III-2: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	other tissues/organs, hypersensitivity reactions, loss of efficacy, development of FVIII inhibitors			
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				
N/A				
Category 3 - Required additional pharmacovigilance activities				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
EUHASS (EUropean HAemophilia Safety Surveillance) registry (study 14149)	The EUHASS registry is an investigator-driven registry that is funded by the European Union (EU) in addition to Bayer and other manufacturers of FVIII concentrate products. EUHASS is a prospective Haemophilia Safety Surveillance System for Europe. Participating centres have agreed to report all relevant AEs in their patients in a prospective manner. Events, that should be reported, are: new inhibitors, infections, allergic reactions, thromboses, new malignancies, and deaths.	Development of FVIII inhibitors Hypersensitivity reactions Potential long-term PEG-related ARs Use in patients with renal insufficiency Use in patients with hepatic impairment	Enrolment of first patient receiving Jivi Quarterly listings Annual report End of data collection Reporting of	Q4 2018 – Q1 2019 One quarter following the end of the reporting period (Upon receipt from EUHASS) Received by MAH 1 year after the end of the reporting period (Upon receipt from EUHASS); Submitted as part of the PSUR. 2027 PSUR based on

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

Table Part III-2: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			study results	annual reports from the registry

AR: Adverse Reaction; EU: European Union; EUHASS: EUropean HAemophilia Safety Surveillance; MAH: Marketing Authorization Holder No: Number; PBRER: Periodic Benefit-risk Evaluation Report; PEG: Polyethylene Glycol; PSUR: Periodic Safety Update Report; SN: Study Number

PART IV: Plans for post-authorisation efficacy studies

Based on available data, there are no identifiable gaps in knowledge about efficacy in the target population and there is no need at this time for further efficacy studies post-authorisation.

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

Risk Minimisation Plan

As for any drug, the identified and potential risks of Jivi need to be carefully weighed against the benefits for each individual patient. The information on Jivi provided in the SmPC, such as indications, dosage recommendations, contraindications, warnings and undesirable effects, provide the healthcare professional and patient with a sound basis for an individualised risk-benefit evaluation and thereby help minimise any safety risks from the use of Jivi.
The majority of the risks identified with BAY Jivi are common to the class of FVIII replacement therapies. The risk that is not shared with other FVIII replacement therapies is the development of anti-PEG antibodies resulting in loss of efficacy and/or hypersensitivity. This risk occurred primarily in patients <6 years of age but can occur in 0-2.0% of patients ≥7 years based on the clinical trial data.

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: development of FVIII inhibitors	**Routine risk communication:** Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation for monitoring FVII inhibitors development by appropriate clinical observations and laboratory tests is included in Section 4.4 Special warnings and precautions for use **Other routine risk minimisation measures beyond the Product Information:** None proposed
Important identified risk: hypersensitivity reactions	**Routine risk communication:** Section 4.3 Contraindications Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Section 4.4 Special warnings and precautions for use **Other routine risk minimisation measures beyond the Product Information:** None proposed

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

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

Safety concern	Routine risk minimisation activities
Important identified risk: loss of efficacy associated with anti-PEG (polyethylene glycol) antibodies	**Routine risk communication:** Section 4.8 Undesirable effects **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Section 4.1 Indication Section 4.2 Posology and method of administration Recommendation on how to detect and manage loss of efficacy associated with anti-PEG antibodies is included in Section 4.4 Special warnings and precautions for use **Other routine risk minimisation measures beyond the Product Information:** None proposed
Important Potential Risks: **Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs**	**Routine risk communication:** Section 5.3 Preclinical safety data **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed due to lack of toxicology findings in non-clinical studies **Other routine risk minimisation measures beyond the Product Information:** None proposed
Important Potential Risk: Off-label Use	**Routine risk communication:** Section 4.1 Therapeutic Indications **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** None proposed
Important Potential Risk: Thromboembolic Events	**Routine risk communication:** Not applicable. In section 4.4 Special Warnings and precautions for use there is a section on cardiovascular events **Routine risk minimisation activities recommending specific clinical**

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

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

Safety concern	Routine risk minimisation activities
	measures to address the risk: None proposed **Other routine risk minimisation measures beyond the Product Information:** None proposed
Missing information: use in patients with severe hepatic impairment	**Routine risk communication:** Not applicable **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** None proposed
Missing information: use in patients with severe renal impairment	**Routine risk communication:** Not applicable **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed **Other routine risk minimisation measures beyond the Product Information:** None proposed
Missing information: use in elderly patients >65 years of age	**Routine risk communication:** Section 4.2 Posology and method of administration A statement regarding the limited experience in the elderly has been added **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None proposed. **Other routine risk minimisation measures beyond the Product Information:** None proposed.

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

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

Safety concern	Routine risk minimisation activities
Missing information: use in women, including pregnancy and lactation	**Routine risk communication:** Section 4.6 Fertility, Pregnancy and lactation **Routine risk minimisation activities recommending specific clinical measures to address the risk:** 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. No additional risk minimisation measures are planned.

V.3 Summary of risk minimisation measures

Table Part V-2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Development of FVIII inhibitors	**Routine risk minimisation measure** • Warning in section 4.4 of the SmPC **Additional risk minimisation measure** • None	**Routine pharmacovigilance** • Follow-up questionnaire for ARs of loss of efficacy **Additional pharmacovigilance activities** • EUHASS registry (study 14149) • Multinational PASS (study 20904)
Hypersensitivity reactions	**Routine risk minimisation measure** • Contraindication in section 4.3 of the SmPC • Warning in section 4.4 of the SmPC **Additional risk minimisation measure** • None	**Routine pharmacovigilance** • Follow-up questionnaire for hypersensitivity reactions **Additional pharmacovigilance activities** • EUHASS registry (study 14149) • Multinational PASS (study 20904)
Loss of efficacy associated with anti-PEG antibodies	**Routine risk minimisation measure** • Section 4.1 Indication • Section 4.2 Posology and	**Routine pharmacovigilance** • Follow-up questionnaire for ARs of loss of efficacy **Additional pharmacovigilance**

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

Table Part V-2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	method of administration • Warning in section 4.4 of the SmPC **Additional risk minimisation measure** • None	**activities** • Multinational PASS (study 20904)
Important Potential Risks		
Off-label use	**Routine risk minimisation measure** • Section 4.1 Indication • Warning in section 4.4 of the SmPC **Additional risk minimisation measure** • None	**Routine pharmacovigilance** • Collection and assessment of reports of off-label use **Additional pharmacovigilance activities** • None
Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs	**Routine risk minimisation measure** • Section 5.3 Preclinical safety data **Additional risk minimisation measure** None	**Routine pharmacovigilance** • Follow-up questionnaires for neurocognitive disorders and development of renal impairment on Jivi **Additional pharmacovigilance activities** • Multinational PASS (study 20904) EUHASS registry (study 14149)
Thromboembolic Events	**Routine risk minimisation measure** • Section 4.4 Special warnings and precautions for use **Additional risk minimisation measure** • None	**Routine pharmacovigilance** • Not applicable **Additional pharmacovigilance activities** • None proposed
Missing Information		
Use in patients with severe hepatic impairment	**Routine risk minimisation measure** • Not applicable **Additional risk minimisation measure** • None	**Routine pharmacovigilance** • None proposed **Additional pharmacovigilance activities** • EUHASS registry (study 14149)
Use in patients with renal	**Routine risk minimisation**	**Routine pharmacovigilance** • Revised Follow-up questionnaire

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

Table Part V-2: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
impairment	**measure** • Not applicable **Additional risk minimisation measure** • None	for ARs **Additional pharmacovigilance activities** • EUHASS registry (study 14149)
Use in women, including pregnancy and breast-feeding	**Routine risk minimisation measure** • Section 4.6 Fertility, pregnancy and lactation **Additional risk minimisation measure** • None	**Routine pharmacovigilance** • None planned **Additional pharmacovigilance activities** • None
Use in elderly patients >65 years of age	**Routine risk minimisation measure** • Section 4.2 Posology and method of administration **Additional risk minimisation measure** • None	**Routine pharmacovigilance** • None proposed **Additional pharmacovigilance activities** • None

AR: Adverse Reaction; EMA: European Medicines Agency; EU: European Union; MAH: Marketing Authorization Holder; EUHASS: EUropean HAemophilia Safety Surveillance; No.: Number; PBRER: Periodic Benefit-Risk Assessment Report; PEG: Polyethylene Glycol; SN: Study Number; >: Greater than.

PART VI: Summary of risk management plan (RMP)

Summary of RMP for Jivi

This is a summary of the RMP for Jivi. The RMP details important risks of Jivi, how these risks can be minimised and how more information will be obtained about risks and uncertainties (missing information).

The SmPC and its package leaflet give essential information to healthcare professionals and patients on how Jivi should be used.

This summary of the RMP 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 the RMP for Jivi.

I. The medicine and what it is used for

Jivi is authorised for indicated for the treatment and prophylaxis of bleeding in previously treated patients (PTPs) aged ≥7 years with haemophilia A (congenital Factor VIII [FVIII] deficiency) (see SmPC for the full indication). It contains damoctocog alfa pegol as the active substance and it is given by injection.

Further information about the evaluation of Jivi's benefits can be found in the EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/jivi.

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

Important risks of Jivi, together with measures to minimise such risks and the proposed studies for learning more about Jivi'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 authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions (ARs) will be collected continuously and regularly analysed, including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report (PBRER/PSUR) assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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

II.A List of important risks and missing information

Important risks of Jivi 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 Jivi. 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).

Table Part VI-1: Summary of safety concerns

Important identified risks	• Development of FVIII inhibitors • Hypersensitivity reactions • Loss of efficacy associated with anti-PEG antibodies
Important potential risks	• Off-label use • Long-term potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs • Thromboembolic events
Missing information	• Use in patients with severe hepatic impairment • Use in patients with renal insufficiency • Use in elderly patients >65 years of age • Safety profile in women including pregnancy and lactation

PEG: Polyethylene Glycol

II.B Summary of important risks

Table Part VI-2: Important identified risk: Development of FVIII inhibitors

Evidence for linking the risk to the medicine	The development of antibodies to FVIII with neutralising properties (known as FVIII inhibitors) may have a great impact on treatment of patients with haemophilia. Therefore, inhibitor development is considered a medically significant event, and it is regarded as the most serious complication of FVIII replacement in patients with haemophilia.
Risk factors and risk groups	Widely accepted risk factors for inhibitor development to FVIII are the severity of the FVIII gene defect, the prior number of exposure days (EDs), haemophilia severity, ethnicity, genotype, inhibitor testing frequency, intensity of treatment and familial predisposition. Other risk factors are still under debate, such as the specific treatment regimen, age at first exposure, mode of administration, surgery, type of FVIII concentrate, concomitant vaccinations and extravasations during injection.
Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Routine pharmacovigilance	Collection of adverse events (AEs) of FVIII inhibition through: Targeted post-marketing questionnaire on loss of drug efficacy that includes information pertaining to FVIII inhibitors. (Refer to **Annex 4.2**)
Additional pharmacovigilance activities	• EUHASS registry (study 14149) • Multinational PASS (study 20904)

EUHASS: EUropean HAemophilia Safety Surveillance; PASS: Post-Authorisation Safety Study.

Table Part VI-3: Important identified risk: Hypersensitivity reactions

Evidence for linking the risk to the medicine	Hypersensitivity reactions have been observed in the clinical trial program. These events are usually mild to moderate in intensity and resolve rapidly upon discontinuation of drug administration.
Risk factors and risk groups	Hypersensitivity reactions have been observed with the first 4 infusions primarily in patients <6 years of age. Hypersensitivity may also be related to an immune response to polyethylene glycol (PEG). In patients ≥7 years the incidence of hypersensitivity reactions associated with anti-PEG antibodies was 0.4%.
Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Routine pharmacovigilance	Collection of adverse events (AEs) of hypersensitivity reactions through: Targeted post-marketing questionnaire on hypersensitivity reactions. (Refer to **Annex 4.1**)

Part VI: Summary of the risk management plan

Table Part VI-3: Important identified risk: Hypersensitivity reactions

Additional pharmacovigilance activities	• EUHASS registry (study 14149) • Multinational PASS (study 20904)

EUHASS: EUropean HAemophilia Safety Surveillance; PASS: Post-Authorisation Safety Study; <: Less than; ≥: Greater than or equal to

Table Part VI-4: Important identified risk: Loss of efficacy associated with anti-PEG antibodies

Evidence for linking the risk to the medicine	Loss of efficacy associated with development of anti-polyethylene glycol (PEG) antibodies has been identified in clinical trials.
Risk factors and risk groups	The risk was only seen in patients 6 years of age and younger. Loss of efficacy associated with development of anti-PEG antibodies has been identified in clinical trials following administration of the 2nd to 4th dose, with no additional cases observed at a later time point.
Risk minimisation measures	**Routine risk minimisation measures** • "Age restriction" • Information provided to healthcare professionals and patients in the existing labelling materials
Routine pharmacovigilance	Collection of adverse events (AEs) of Loss of drug efficacy associated with anti-PEG antibodies through: • Targeted post-marketing questionnaires on loss of efficacy. (Refer to **Annex 4.2**)
Additional pharmacovigilance activities	• Multinational PASS (study 20904)

PASS: Post-Authorisation Safety Study.

Table Part VI-5: Important potential risk: Off-label use

Evidence for linking the risk to the medicine	Age <6 years has been determined during the clinical trials to be a risk factor for development of anti-PEG immunoglobulin M (IgM) antibodies following exposure to Jivi. Development of these antibodies is associated with the clinical events of loss of efficacy/hypersensitivity. In order to minimise the risk of these events, the population has been restricted to Haemophilia A patients age ≥7 years.
Risk factors and risk groups	Age <7 years
Risk minimisation measures	**Routine risk minimisation measures** • Collection of cases of off-label use.

PEG: Polyethylene Glycol; <: Less than; ≥: Greater than or equal to

Part VI: Summary of the risk management plan

Table Part VI-6: Important potential risk: Long-term potential effects of polyethylene glycol (PEG) accumulation in the choroid plexus of the brain and other tissues/organs

Evidence for linking the risk to the medicine	Accumulation of PEG in the choroid plexus has been demonstrated in non-clinical studies of other products at much higher doses of PEG than with Jivi. There is no evidence from the non-clinical studies with Jivi or from the PEG plasma level at steady state for clinically relevant accumulation of PEG in tissues.
Risk factors and risk groups	Very young patients could potentially be more impacted by high levels of PEG.
Risk minimisation measures	Information provided to healthcare professionals in the labelling materials is proposed.
Routine pharmacovigilance	Targeted post-marketing questionnaires on the development of renal impairment (refer to **Annex 4.4**: Questionnaire – Renal impairment/failure) during Jivi treatment and on neurocognitive disorders. (Refer to **Annex 4.3**: Questionnaire – Neurocognitive disorders)
Additional pharmacovigilance activities	• Multinational PASS (study 20904) • EUHASS registry (study 14149)

EUHASS: EUropean HAemophilia Safety Surveillance; PASS: Post-Authorisation Safety Study; PEG: Polyethylene Glycol.

Table Part VI-7: Important Potential risk: Thromboembolic events

Evidence for linking the risk to the medicine	No cases reported in the clinical program.
Risk factors and risk groups	Patients with existing cardiovascular risk factors have the potential for thromboembolic events when FVIII levels are normalized.
Risk minimisation measures	Information provided to healthcare professionals and patients in the existing labelling materials.

Table Part VI-8: Missing information: Use in patients with severe hepatic impairment

Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Additional pharmacovigilance activities	• EUHASS registry (study 14149)

Part VI: Summary of the risk management plan

Table Part VI-9: Missing information: Use in patients with renal insufficiency

Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Additional pharmacovigilance activities	• EUHASS registry (study 14149)

Table Part VI-10: Missing information: Use in elderly patients >65 years of age

Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Additional pharmacovigilance activities	None

Table Part VI-11: Missing information: Safety profile in women including pregnancy and lactation

Risk minimisation measures	No additional risk minimisation activities beyond the information provided to healthcare professionals and patients in the labelling materials are proposed.
Additional pharmacovigilance activities	None

II.C Post-authorisation development plan

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

Table Part VI-12: Studies which are conditions of the marketing authorisation

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				
Multinational non-interventional PASS Study 20904 HA-SAFE	To provide long-term safety data to investigate safety risks associated with Jivi use for prophylaxis in the real-world settings, including the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, hypersensitivity reactions, loss of efficacy, development of FVIII inhibitors.	Potential long-term PEG-related Ars Hypersensitivity reactions Loss of efficacy associated with anti-PEG antibodies Development of FVIII inhibitors.	First patient first visit Study completion by Study report by	Q2/2021 Q2/2028 Q4/2028
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				
N/A				

AR: Adverse Reaction; N/A: Not Applicable; PASS: Post-Authorisation Safety Study; PEG: Polyethylene Glycol.

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

Table Part VI-13: Other studies in post-authorisation development plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Epidemiological study	EUHASS registry (study 14149) The EUHASS registry is an investigator-driven registry that is funded by the EU in addition to Bayer and other manufacturers of FVIII concentrate products. EUHASS is a prospective Haemophilia Safety Surveillance System for Europe. Participating	Development of FVIII inhibitors Hypersensitivity reactions Potential long-term PEG-related ARs	Enrolment of first patient receiving Jivi Quarterly listings	Q4 2018 – Q1 2019 One quarter following the end of the reporting period (Upon

Table Part VI-13: Other studies in post-authorisation development plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
	centres have agreed to report all relevant AEs in their patients in a prospective manner. Events, that should be reported, are: new inhibitors, infections, allergic reactions, thromboses, new malignancies and deaths.	Use in patients with renal insufficiency Use in patients with hepatic impairment		receipt from EUHASS)
			Annual report	Received by MAH 1 year after the end of the reporting period (Upon receipt from EUHASS)' Submitted as part of the PSUR
			End of data collection	2027
			Reporting study results	PSUR based on annual reports from the registry

AE: Adverse Event; EU: European Union; MAH: Marketing Authorization Holder; EUHASS: EUropean HAemophilia Safety Surveillance; No.: Number; PBRER: Periodic Benefit-Risk Assessment Report; PEG: Polyethylene Glycol; PSUR: Periodic Safety Update Report; SN: Study Number.

PART VII: Annexes

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Annex 4 – Specific AE follow-up forms

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Annex 4.1: Questionnaire – Hypersensitivity

Questionnaire for Health Care Professionals concerning a potential Hypersensitivity Reaction reported in association with Jivi®

Bayer

SECTION I- REFERENCE ID		
BAYER CASE ID:	**STUDY ID:**	**PATIENT ID:**
SECTION II- REPORTER/PATIENT INFORMATION		
REPORTER: ☐ **Physician** ☐ **Nurse** ☐ **Other (specify):**_____		
REPORTER CONTACT INFORMATION		
Name:		
Institution/Practice Name:		
Phone:	**Fax:**	
Address:		
Email:		
PATIENT INFORMATION		
Patient Initials *(leave empty for study participants):*	**Age** *(at onset of event)* **or Year of birth:**	**Gender: M/ F**
Height (cm/inches)	**Weight (kg/lbs)**	**Lot number:**
SECTION III- PRODUCT INFORMATION - (INSERT PRODUCT NAME)		
Start Date *(dd/mm/yyyy)*:	**Stop Date** *(dd/mm/yyyy)*:	
Indication *(prophylaxis/on demand)*:		

SECTION IV- EVENT RELATED INFORMATION:

Hypersensitivity Event

1. When was this event diagnosed: _____ DD/ MON/ YEAR

2. Please list all the clinical and laboratory data pertinent to the hypersensitivity reaction in the table below. Please include:
   - A description of the event including symptom severity and the extent of organ involvement.
   - Vital signs (BP, pulse) and physical signs (wheezing, sweating)
   - Diagnostic tests and treatments

Examples are provided in (*parenthesis*)

Organ System	Symptoms & Signs (vital signs and physical signs and symptoms)	Severity (mild, moderate, severe) and extent of involvement	Diagnostic Tests	Treatment
Dermatological and Mucosal	*(pruritis, rash)*	*(moderate, at injection site)*		

Cardiovascular	*(dizziness, hypotension)*	*(mild)*		
Respiratory	*(shortness of breath, tachypnea)*	*(mild, transient)*		
Gastrointestinal	*(nausea)*	(Moderate, 2-3 hs)		
Other				
Other				

Please provide a detailed event description

_____

_____

_____

_____

_____

_____

3. Time from start of Jivi administration to onset of first hypersensitivity symptom.

☐ <15 minutes ☐ 15-59 minutes ☐ 1-<4 hours ☐ 4-24 hours ☐ >24 hours

4. If the hypersensitivity reaction occurred in temporal relationship to the administration of Jivi, please check the severity that best describes the event.

☐ Grade 1: Mild transient reaction: infusion interruption not indicated; intervention not indicated

☐ Grade 2: Therapy or infusion interruption indicated; but responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids) or interruption of infusion alone; prophylactic medications

indicated for ≤ 24 hours.

☐ Grade 3: Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion). Recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae.

☐ Grade 4: Life-threatening consequences; urgent intervention indicated

5. Please check the status/outcome that best describes the hypersensitivity event:

☐ Recovered without Sequelae/Resolved ☐ Recovered with Sequelae

☐ Recovering ☐ Not recovered – Ongoing treatment ☐ Unknown ☐ Death

6. Was the event/signs or symptoms observed by a healthcare professional?

☐ Yes ☐ No

If yes, please specify the type of HCP (nurse, pharmacist, physician)_____

7. If known, provide number of exposure days (ED) with JIVI: _____

If unknown, classify according to category:

☐ 0 – 4 ED ☐ 5 – 19 ED ☐ 20 – 49 ED

☐ 50 – 100 ED ☐ >100 ED ☐ Not known

8. Relevant medications and vaccinations. Please list the following:

A. Concomitant medications at the time of the hypersensitivity event

_____

B. All PEGylated medications that the patient has been exposed to at any time

_____

C. All vaccinations administered during the previous 6 months

_____

Previous exposure:

9. Has the patient ever been treated with other FVIII products? ☐ Yes ☐ No

If YES: Provide therapy date(s) of exposure(s), specify brand name if possible:

Name of drug taken	Date of initial	Date of final exposure	Reason for discontinuation

	exposure (Month/Day/Year)	(Month/Day/Year)	

10. Has the patient encountered hypersensitivity with previous administration of Jivi, a prior factor VIII treatment or to any of the drugs mentioned in questions #8? ☐ Yes ☐ No
    If YES, provide the name of the drug and a description of the symptoms:

11. Medical History

- Does this patient have any known hypersensitivities/allergies? ☐ Yes ☐ No
  (medicines, cosmetics, food, chemicals, plants, during surgical procedures, others)

If yes, please list the suspected product name and specify the signs/symptoms associated with these hypersensitivities

_____

_____

- Does the patient suffer from any atopic diseases (e.g. asthma, allergic rhinitis, endogenous eczema, etc)?
  ☐ Yes, please complete the table below ☐ No

Atopic disease	Severity (mild, moderate, severe)	Signs/Symptoms including extent of disease (localised or generalised)	Are signs and symptoms chronic or intermittent	Duration (years)

Has treatment been provided for these atopic diseases during the past 12 months? ☐ Yes ☐ No

If treatment has been provided for these atopic diseases within the past 12 months, please provide the information in the table below regarding medication use.

Name of drug taken, dose and route of administration	Date of initial treatment (Month/Day/Year)	Status: Ongoing or date of final exposure (Month/Day/Year)	Reason for treatment initiation

Reporter:

NAME: _____ TITLE: _____ SIGNATURE: _____ DATE: ___ /___ / _

Thank you for completing this form! The information provided is very valuable for us and for all patients undergoing treatment with Jivi.

Annex 4.2: Questionnaire – LODE and inhibitor

Questionnaire for Health Care Professionals concerning a potential loss of drug effect (LODE) reported in association with Jivi®

Bayer

SECTION I- REFERENCE ID		
BAYER CASE ID:	**STUDY ID:**	**PATIENT ID:**
SECTION II- REPORTER/PATIENT INFORMATION		
REPORTER: ☐ **Physician** ☐ **Nurse** ☐ **Other (specify):** _____		
REPORTER CONTACT INFORMATION		
Name:		
Institution/Practice Name:		
Phone:	**Fax:**	
Address:		
Email:		
PATIENT INFORMATION		
Patient Initials *(leave empty for study participants):*	**Age** *(at onset of event)* **or Year of birth:**	**Gender: M/ F**
Height (cm/inches):	**Weight (kg/lbs):**	**Lot number:**
SECTION III- PRODUCT INFORMATION - (INSERT PRODUCT NAME)		
Start Date *(dd/mm/yyyy)*:	**Stop Date** *(dd/mm/yyyy)*:	
Indication *(prophylaxis/on demand)*:		
SECTION IV- EVENT RELATED INFORMATION		

1. When was this event diagnosed: _____ DD/ MON/ YEAR

2. Check the description which best describes the event being reported

   ☐ LODE due to confirmed FVIII inhibitor
   ☐ LODE with negative results for a FVIII inhibitor (Bethesda Units < 0.6)
   ☐ LODE without assessment of a FVIII inhibitor

3. If known, provide number of exposure days (ED) to Jivi prior to the event: _____
   If unknown, classify according to category: ☐ 0 – 4 ED ☐ 5 – 19 ED ☐ 20 – 49 ED
   ☐ 50 – 100 ED ☐ >100 ED ☐ Not known

4. Provide the Factor VIII recovery level with Jivi and the corresponding date for the most recent test performed **PRIOR** to the diagnosis of LODE:

Jivi administration: Date_____ (hour/minute)_____

	Trough or Pre-Administration FVIII level	Peak (15-60 minutes of administration) or Post Administration FVIII level	Dose in IU/Kg or total dose administered	FVIII Recovery (% increase per IU per kg)
Date/Time				
FVIII level (IU/dL) or %				

☐ None available

5. Provide the Factor VIII recovery level with Jivi and the corresponding date for the most recent test performed **AFTER** LODE was diagnosed, or that resulted in the diagnosis of LODE:

Jivi administration: Date_____ (hour/minute)_____

	Trough or Pre-Administration FVIII level	Peak or Post Administration FVIII level	Dose in IU/Kg or total dose administered	FVIII Recovery % increase per IU/kg)
Date/Time				
FVIII level (IU/dL or %)				

☐ None available

Switch from Jivi to another FVIII product

6. **Please provide the recovery observed with the other FVIII product used after diagnosis of LODE with Jivi**

FVIII administration: Date_____ (hour/minute)_____

	Trough or Pre-Administration FVIII level	Peak or Post Administration FVIII level	Dose in IU/Kg or total dose administered	FVIII Recovery % (kg/dL)
Date/time				
FVIII level (IU/dL)				

☐ None available ☐ Not applicable / Jivi continued (product not switched)

7. Which was / were the reasons for LODE or suspicion of inhibitor development? (Check all that apply)
   - ☐ Reduced recovery and/or reduced half life
   - ☐ Higher dose than usual was needed to achieve therapeutic effect
   - ☐ Patient report only (No objective reason)
   - ☐ Bleeding event

   If a reason was a bleeding event, please indicate which apply.
   - ☐ (On demand) Bleed did not stop as expected after treatment
   - ☐ (On prophylaxis) Increased number of breakthrough bleeds
   - ☐ (On prophylaxis) unexpected bleed after prophylaxis infusion,

   Please provide the time between Jivi administration and the bleeding event _____(hours)

   ☐ Other reason(s):

_____

For patients with LODE due to a confirmed FVIII inhibitor (Questions 8-10)

8. Please provide the following information regarding FVIII inhibitors during the time periods:
   a. Prior to Jivi use
   b. During Jivi use
   c. After discontinuation of Jivi

Time Period	FVIII Product Name	Inhibitor Level / not detected / unknown	Date (use dd/mm/yyyy format)	Assay Method: Bethesda or Nijmegen modified Bethesda
Prior to Jivi use (most recent products) **(Product 1)** Titer at first detection*				
Maximal titer detected				
Most recent titer				
Prior to Jivi use **(Product 2)** Titer at first detection*				
Maximal titer detected				
Most recent titer				
During Jivi use Titer at first detection*				
Maximal titer detected				
Most recent titer				
After Jivi discontinuation Titer at first detection*				
Maximal titer detected				
Most recent titer				

*If titer at first detection is not available, please report that first available titer on the specific FVIII product.

Please provide any other pertinent information relating to inhibitors including episodes on products not included in the above table (e.g. immune tolerance therapy).

_____

_____

_____

Questionnaire for Health Care Professionals concerning a potential loss of drug effect (LODE) reported in association with Jivi®

RESPONDER:

NAME: _____ TITLE: _____ SIGNATURE: _____ DATE: ___ /___ / _____

Thank you for completing this form! The information provided is very valuable for us and for all patients undergoing treatment with Jivi®.

Annex 4.3: Questionnaire – Neurocognitive disorders

Questionnaire for Health Care Professionals concerning a potential event of a Neurocognitive Disorder reported in association with Jivi®

Bayer

SECTION I- REFERENCE ID		
BAYER CASE ID:	**STUDY ID:**	**PATIENT ID:**

SECTION II- REPORTER/PATIENT INFORMATION
REPORTER: ☐ **Physician** ☐ **Nurse** ☐ **Other (specify):** _____

REPORTER CONTACT INFORMATION		
Name:		
Institution/Practice Name:		
Phone:		**Fax:**
Address:		
Email:		

PATIENT INFORMATION			
Patient Initials *(leave empty for study participants):*	**Age** *(at onset of event)* **or Year of birth:**		**Gender: M/ F**

SECTION III- PRODUCT INFORMATION - (INSERT PRODUCT NAME)	
Start Date *(dd/mm/yyyy)*:	**Stop Date** *(dd/mm/yyyy)*:

Indication ☐ Primary prophylaxis ☐ Secondary prophylaxis ☐ On demand ☐ Unknown

Percent of normal FVIII activity

☐ Severe (<1%) ☐ Moderate (1-5%) ☐ Mild (<5%)

Dosing Regimen and Exposure days

Bayer

Dosing regimen: _____IU/kg

☐ 2x /week ☐ Every 5 days ☐ Every 7 days ☐ Unknown ☐ On demand

Exposure days

☐ 0-19 ☐ 20-49 ☐ 50-99 ☐ > 100 ☐ Unknown

Start (DD/MM/YY):___/___/___ ☐ Unknown

Stop (DD/MM/YY):___/___/___ ☐ Unknown

Jivi® was discontinued due to the event ☐ Yes ☐ No ☐ Unknown

Jivi® was restarted after the event ☐ Yes ☐ No ☐ Unknown

Jivi® dose changed ☐ Yes, please specify daily dose ____IU/kg ☐ No ☐ Unknown

And start date: ___/___/___

SECTION IV- EVENT RELATED INFORMATION

Neurocognitive related adverse event (Please specify the event)_____			
Start/Stop Dates	**Start** (DD/MM/YY)___/___/___☐ Unknown **Stop** (DD/MM/YY)___/___/___ ☐ Unknown		
Affected neurological or psychiatric domains	☐ Memory ☐ Attention ☐ Other(Please specify) _____	☐ Learning ☐ Language	☐ Perception ☐ Social cognition
Cognitive Screening Test	☐ Mini-Mental State Examination (MMSE)	☐ Montreal Cognitive Assessment (MOCA)	Mini-Cog

Bayer

Results	☐ Normal	☐ Abnormal	
Neuroimaging	☐ MRI	☐ CT	☐ Other
Results	Description:		
Outcome	☐ Recovered	☐ Recovering	☐ Recovered with sequelae
	☐ Not recovered	☐ Unknown	☐ Fatal Autopsy ☐yes ☐no ☐Unknown
Treatment	☐ None ☐ Unknown ☐ Yes; Please specify _____		

Relevant Medical History / Risk Factors (please check all relevant boxes)			
Family history of neurological disorder including seizures, cognitive disorder, cerebral autoimmune disease, stroke, hydrocephalus, etc.	☐ Unknown	☐ No	☐ Yes Please specify:
Cardiovascular disease: **If yes please specify;** **_____**	☐ Unknown	☐ No	☐ Yes Onset date: _____
Stroke	☐ Unknown	☐ No	☐ Yes Onset date: _____
Psychiatric disease: **If yes please specify;** **_____**	☐ Unknown	☐ No	☐ Yes Onset date: _____

Obstructive sleep apnea	☐ Unknown	☐ No	☐ Yes Onset date: _____
Diabetes mellitus type I or type II **If yes please specify;** _____	☐ Unknown	☐ No	☐ Yes Onset date: _____
Autoimmune disease **If yes please specify;** _____	☐ Unknown	☐ No	☐ Yes Onset date: _____
Active malignancy **If yes please specify;** _____	☐ Unknown	☐ No	☐ Yes Onset date: _____
Head injury	☐ Unknown	☐ No	☐ Yes Onset date: _____
Smoking	☐ Unknown	☐ No	☐ Yes Onset date: _____
Heavy consumption of alcohol	☐ Unknown	☐ No	☐ Yes Onset date: _____
Other **If yes please specify;**	☐ Unknown	☐ No	☐ Yes Onset date:

_____			_____

Concomitant Medication	Start Date DD/MM/YY	Stop Date DD/MM/YY	Ongoing
☐ anti-depressants and neuroleptics Please specify:			☐ Yes ☐ No ☐ Unknown
☐ anti-cholinergic drugs Please specify:			☐ Yes ☐ No ☐ Unknown
☐ anti-histamines Please specify:			☐ Yes ☐ No ☐ Unknown
☐ Herbal substances Please specify:			☐ Yes ☐ No ☐ Unknown
☐ Other PEGylated drug Please specify:			☐ Yes ☐ No ☐ Unknown
☐ Other Please specify:			☐ Yes ☐ No ☐ Unknown
☐ Other Please specify:			☐ Yes ☐ No ☐ Unknown
☐ Other			☐ Yes ☐ No ☐ Unknown

Please specify:			

Please enclose copies of all relevant information pertaining to the adverse event (e.g. hospital summary, results of diagnostic tests etc.)

Annex 4.4: Questionnaire – Renal impairment/failure

Questionnaire for Health Care Professionals concerning a potential event of Renal Impairment reported in association with Jivi®

Bayer

SECTION I- REFERENCE ID		
BAYER CASE ID:	**STUDY ID:**	**PATIENT ID:**

SECTION II- REPORTER/PATIENT INFORMATION
REPORTER: ☐ **Physician** ☐ **Nurse** ☐ **Other (specify):** _____

REPORTER CONTACT INFORMATION		
Name:		
Institution/Practice Name:		
Phone:		**Fax:**
Address:		
Email:		

PATIENT INFORMATION			
Patient Initials *(leave empty for study participants):*	**Age** *(at onset of event)* **or Year of birth:**		**Gender: M/ F**
Height (cm/inches)	**Weight (kg/lbs)**		**Lot number:**

SECTION III- PRODUCT INFORMATION - (INSERT PRODUCT NAME)	
Start Date *(dd/mm/yyyy)*:	**Stop Date** *(dd/mm/yyyy)*:
Indication *(prophylaxis/on demand)*:	

SECTION IV- EVENT RELATED INFORMATION

1. **Medical History / Risk Factors for Renal Disease** (Please tick all that apply)

Pre-existing chronic kidney disease	☐ Yes Please specify suspected	Duration	☐ No	☐ Unknown

Bayer

	cause(s) _____ _____			
Hypertension	☐ Yes	Duration	☐ No	☐ Unknown
Diabetes mellitus Type I or Type II (if yes, please specify:_____)	☐ Yes	Duration	☐ No	☐ Unknown
Glomerulonephritis	☐ Yes Please specify suspected cause	Duration	☐ No	☐ Unknown
Interstitial nephritis	☐ Yes Please specify suspected cause	Duration	☐ No	☐ Unknown
Pyelonephritis	☐ Yes	Number of events Number of events requiring hospitalization Date of most recent event	☐ No	☐ Unknown
Infection within the previous 30 days	☐ Yes Please specify	Treatment	☐ No	☐ Unknown

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Autoimmune disease	☐ Yes Please specify	Duration	☐ No	☐ Unknown
Malignancy for which treatment is ongoing (include treatments given at intervals such as monthly)	☐ Yes Please specify	Date of Diagnosis	☐ No	☐ Unknown
Previous treatment for a malignancy	☐ Yes Please specify	Date of Diagnosis	☐ No	☐ Unknown
Surgery on the urinary tract (including treatment of malignancies, malformation and other findings)	☐ Yes Please specify	Date of Diagnosis Date of Surgery	☐ No	☐ Unknown
Other Surgical procedures within the past 90 days. (if yes, please specify: Procedure 1 Type of surgery:_____ Type of anesthesia:_____ Hypotension during surgery:_____ Other (please specify:			☐ No	☐ Unknown
Procedure 2 Type of surgery:_____ Type of anesthesia:_____ Hypotension during surgery:_____			☐ No	☐ Unknown

Bayer

Other (please specify: _____		
Other relevant History		

2. **RENAL-RELATED ADVERSE EVENT** (please specify adverse event) _____	
Start/stop date	Start (DD/MM/YY): ____/____/____ ☐ Unknown Stop (DD/MM/YY): ____/____/____ ☐ Unknown
Symptoms and signs of renal injury	☐ Oliguria ☐ Anuria ☐ Dysuria ☐ Polyuria ☐ Hematuria ☐ Flank/Back pain ☐ Fever ☐ Hyperter ☐ Other (e.g. edema) please specify_____
Diagnostic procedures	☐ Ultrasound ☐ MRI ☐ CT ☐ Renal biopsy Results: Please include final diagnosis.
Treatment	Please list all treatments provided (Medications, diet, fluids, dialysis other) that are pertinent to renal function. _____ ☐ None ☐ Unknown
Outcome	☐ Recovered ☐ Recovering ☐ Recovered with sequelae ☐ Not recovered ☐ Unknown ☐ Fatal (autopsy: ☐Yes ☐ No ☐Unknown) If yes, please provide results

Please provide a detailed description of the renal event:

_____

_____

_____

_____

3. **Jivi® treatment (dosing regimen and exposure days)**

A. Start Date (DD/MM/YY): ___/ ___/___/ ☐ Unknown
Stop Date (DD/MM/YY): ___/ ___/___/ ☐ Unknown

B. Dosing regimen at time of event or immediately prior to the event: Dose _____IU/kg

Frequency of administration: ☐ 2x /week ☐ every 5 days ☐ every 7 days ☐ Unknown ☐ on demand

C. If known, provide number of exposure days to Jivi (ED): _____

If unknown, classify according to category: ☐ 0 – 4 ED ☐ 5 – 19 ED ☐ 20 – 49 ED
☐ 50 – 100 ED ☐ >100 ED ☐ Not known

D. Modifications to Jivi dosing regimen

Jivi® was discontinued due to the event ☐ Yes ☐ No ☐ Unknown

Jivi® dose **was** changed due to the event ☐ Yes ☐ No ☐ Unknown

If yes, please specify new dosing regimen (post event)

Start date: ___/___/___/

Dose: IU/kg _____ Dosing frequency _____

If another FVIII therapy was initiated, please specify: _____

E. Concomitant Medication

Please pay special attention to any drugs/substances used within the past 90 days with known renal side

effects such as:

Name of drug	Total daily dose	Start date DD/MM/YY	Stop date DD/MM/YY	Ongoing
☐ NSAIDs				☐ Yes ☐ No ☐ Unk
☐ ACE inhibitors (please specify_____)				☐ Yes ☐ No ☐ Unk
☐ Contrast agents (please specify_____)				☐ Yes ☐ No ☐ Unk
☐ Antibiotics (please specify_____)				☐ Yes ☐ No ☐ Unk
☐ Cancer therapy (please specify_____)				☐ Yes ☐ No ☐ Unk
☐ Herbal substances (please specify_ _____)				☐ Yes ☐ No ☐ Unk
☐ Other PEGylated drug (e.g. Cimzia) (please specify_____)				☐ Yes ☐ No ☐ Unk
☐ Others (please specify_____)				☐ Yes ☐ No ☐ Unk

F. Laboratory data (please fill in or enclose copies of relevant lab data results) Please indicate the units used in the laboratory.

		Before Start of Drug	On Jivi prior to event	Date of the Renal event	Greatest Renal impairment	Period of resolution	Most recent value	

Lab Test:	Units /Normal range	__/__/__ dd/MM/yy	__/__/__ dd/MM/yy	__/__/__ dd/MM/yy	__/__/__ dd/MM/yy	__/__/__ dd/MM/yy	__/__/__ dd/MM/yy	
Creatinine								
GFR								
Urea								
Potassium (K)								
Sodium (Na)								
Phosphate								
Calcium								
Albumin								
CRP								
Leukocytes								
LDH								
Urinary Analysis / Sediment: ☐ not done								
Proteinuria								☐ Yes ☐ No ☐ Unk
Hematuria								☐ Yes ☐ No ☐ Unk
Leukocyturia								☐ Yes ☐ No ☐ Unk
Erythrocytes								☐ Yes ☐ No ☐ Unk
Casts/ other								☐ Yes ☐ No ☐ Unk

Other relevant Lab- Data: (e.g., antibodies, urinary or serum eosinophils etc.)

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_____Date: __/__/__

_____Date: __/__/__

Please enclose also copies of all relevant information (e.g. hospital summary, results of diagnostic tests, histopathology of renal biopsy etc.).

Signature : _____ Date : _____

SECTION IV A- RELEVANT CLINICAL SYMPTOMS *(to AE of Interest)*

Symptom		Symptom	
e.g. Chest pain	☐		☐
	☐		☐
	☐		☐
	☐		☐

Additional Clinical Information:

SECTION IV B- RELEVANT FAMILY HISTORY*(to AE of Interest) (for immediate family member only)*

Bayer

Condition *(Enter the conditions)*		Condition	
e.g. High Blood Pressure	☐		☐
	☐		☐
	☐		☐
	☐		☐

SECTION V- RELEVANT CONCOMITANT MEDICATION

Drug Name	Start date	Stop date	Daily dose	Indication
☐				
☐				
☐				
☐				

SECTION Va- RELEVANT MEDICAL CONDITIONS/HISTORY

Condition	Start Date	Stop Date	Ongoing
☐			☐
☐			☐
☐			☐
☐			☐

SECTION VI- RELEVANT DIAGNOSTICS/LAB TESTS

Name of the Test	Date of Test	Result
e.g. X-Ray performed ☐		
☐		
☐		

Bayer

☐		

SECTION VIII: ADDITIONAL INFORMATION (COMMENTS) *(if any): This section can also be used to provide information on any of the sections above. Please note the relevant section number below.*

Annex 4.5: Follow-up questionnaires User Guidance

Damoctocog alfa pegol (Jivi) FOLLOW-UP QUESTIONNAIRES
USER GUIDANCE

Development of Factor VIII inhibitors - MedDRA terms

PTs: Acquired haemophilia with anti FVIII, XI, or XIII, Anti factor VIII antibody increased, Anti factor VIII antibody positive, Anti factor VIII antibody test, Antibody test abnormal, Antibody test positive, Coagulation factor VIII level abnormal, Coagulation factor VIII level decreased, Coagulation factor decreased, Coagulation factor inhibitor assay, Drug effect decreased, Drug effect delayed, Drug effect incomplete, Drug effect variable, Drug half-life reduced, Drug ineffective, Drug ineffective for unapproved indication, Drug level below therapeutic, Drug level decreased, Drug resistance, Drug-specific antibody present, Drug tolerance, Drug tolerance increased. Factor VIII inhibition, Haemophilia A with anti factor VIII, Inhibiting antibodies, Inhibiting antibodies positive, Inhibitory drug interaction, Neutralising antibodies, Neutralising antibodies positive, No reaction on previous exposure to drug, No therapeutic response, Non-neutralising antibodies, Therapeutic product ineffective, Therapeutic product ineffective for unapproved indication, Therapeutic response changed, Therapeutic response decreased, Therapeutic response delayed, Treatment failure

Hypersensitivity reactions - MedDRA terms

AEs coded to a PT belonging to drug hypersensitivity, hypersensitivity, type I hypersensitivity, type II hypersensitivity, type IV hypersensitivity reaction, documented hypersensitivity to administered product or infusion related reaction are considered to be AEs possibly related to drug hypersensitivity reactions (MedDRA Version27.1). Hypersensitivity reaction is an LLT that codes to the PT of hypersensitivity.

Clinical response characterised by loss of efficacy associated with anti- PEG antibodies - MedDRA terms

For post-marketing surveillance, MedDRA search terms for loss of drug efficacy due to anti-drug antibodies will include the following PTs: drug ineffective, drug-specific antibody present anti-Factor VIII antibody positive, and drug effect decreased. Additional cases may be identified during assessor review of bleeding events with low FVIII recovery.

Renal Impairment – MedDRA terms

PTs of: Renal impairment, acute kidney injury, anuria, oliguria, renal failure, renal injury.

Neurocognitive disorders – MedDRA terms

PTs of: memory impairment, amnesia, cognitive disorder, disturbance in attention, mental impairment, change in sustained attention.

Annex 6 – Details of proposed additional risk minimisation activities

Risk Minimisation activities for Jivi consist of:

- The SmPC (routine)