25 April 2025
EMA/196680/2025
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Jivi

International non-proprietary name: Damoctocog alfa pegol

Procedure No. EMEA/H/C/004054/II/0034

Note

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

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List of abbreviations

ABR	Annualized bleed rate
ADA	Anti-drug antibody
ADR	Adverse drug reaction
AE(SI)	Adverse event (of special interest)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BU	Bethesda units
CL	Clearance
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
ED(s)	Exposure day(s)
EFF	Efficacy analysis set
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EPD	Electronic patient diary
FVIII	Human coagulation factor VIII
Ig	Immunoglobulin
IU	International units
kDa	Kilodalton
LoE	Loss of efficacy
LLOQ	Lower limit of quantification
MAH	Marketing authorization holder
PEG	Polyethylene glycol
PK	Pharmacokinetic
PMI	Post-Marketing Investigation
PRO	Patient-reported outcomes
PT	MedDRA Preferred Term
PTPs	Previously treated patients
PUPs	Previously untreated patients
QoL	Quality of life
rFVIII	Recombinant human factor VIII
SAE	Serious adverse event
SAF	Safety analysis set
SOC	MedDRA System Organ Class
TE(S)AE	Treatment-emergent (serious) adverse event
WFH	World federation of haemophilia

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Bayer AG submitted to the European Medicines Agency on 10 October 2024 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment and prophylaxis of bleeding in previously treated patients ≥7 years of age with haemophilia A for JIVI, based on integrated analysis results from Part A of the Alfa-PROTECT study (21824) and PROTECT Kids main study (15912). Alfa-PROTECT is a Phase 3, single-group treatment, open-label study to evaluate the safety of BAY 94-9027 infusions for prophylaxis and treatment of bleeding in previously treated children aged 7 to <12 years with severe haemophilia A. PROTECT Kids is a multi-center, Phase 3, non-controlled, open-label trial to evaluate the pharmacokinetics, safety, and efficacy of BAY 94-9027 for prophylaxis and treatment of bleeding in previously treated children (age <12 years) with severe haemophilia A. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.3 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision PIP P/0195/2017, on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0195/2017 was completed.

The PDCO issued an opinion on compliance for the PIP P/0195/2017.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: N/A Co-Rapporteur: Ewa Balkowiec Iskra (acting on behalf of the Rapporteur)

Timetable	Actual dates
Submission date	10 October 2024
Start of procedure:	2 November 2024
CHMP Rapporteur Assessment Report	20 December 2024
PRAC Rapporteur Assessment Report	30 December 2024
PRAC Outcome	16 January 2025
CHMP members comments	
Updated CHMP Rapporteur(s) (Joint) Assessment Report	23 January 2025
Request for supplementary information (RSI)	30 January 2025
CHMP Rapporteur Assessment Report	24 March 2025
PRAC Rapporteur Assessment Report	24 March 2025
PRAC members comments	2 April 2025
Updated PRAC Rapporteur Assessment Report	4 April 2025
PRAC outcome	10 April 2025
CHMP members comments	14 April 2025
Updated CHMP Rapporteur Assessment Report	16 April 2025
CHMP Opinion	25 April 2025
The CHMP adopted a report on similarity of Jivi with Altuvoct and Roctavian on date	25 April 2025

2. Scientific discussion

2.1. Introduction

Jivi is approved for the treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with haemophilia A (congenital factor VIII deficiency). Restriction of the indication to patients older than 12 years was due to safety concerns regarding potential effects of long-term polyethylene glycol (PEG) exposure. To support the proposed extension of the indication to previously treated patients ≥ 7 years of age, the MAH provided results of the Alfa-PROTECT Study, the integrated analysis of Alfa-PROTECT Part A and the PROTECT Kids main study which included data from patients aged 7 to <12 years, focusing on the incidence of immune response to PEG within the first 4 exposure days and its impact on treatment efficacy. Moreover, data from PROTECT Kids extension study and PROTECT VIII extension study were provided.

2.1.1. Problem statement

Disease or condition

Haemophilia A (congenital factor VIII [FVIII] deficiency) is a potentially life-threatening or seriously debilitating chronic disease. It is an inherited disease caused by mutations in the gene coding for FVIII which result in FVIII deficiency state.

Claimed therapeutic indication

The proposed therapeutic indication is treatment and prophylaxis of bleeding in previously treated patients ≥ 7 years of age with haemophilia A (congenital factor VIII deficiency).

Epidemiology and risk factors, screening tools/prevention

Haemophilia A is clinically characterised by recurrent bleeding into tissue and joints leading to progressive joint destruction. The disease occurs worldwide with an estimated incidence of 1 to 2 in 10,000 births, affecting predominantly males.

Clinical presentation, diagnosis and stage/prognosis

Haemophilia A is usually diagnosed by measuring FVIII clotting activity (FVIII:C) level in the plasma of a patient. There is a direct correlation between FVIII activity levels and clinical manifestations. Haemophilia A is defined as severe if the plasma FVIII:C level (measured as IU/dL) is < 1%, moderate if it is between 1% and 5%, and mild if it is between > 5% and 40% of normal.

Haemophilia A can result in spontaneous and life-threatening bleeding events or excessive bleeding in response to trauma. Bleeds occur in muscle, central nervous system, organs, soft tissue and most frequently in joints, which leads to joint damage and severe disability, with major effects on the physical, psychosocial, quality of life, and financial conditions of the haemophilia patients.

Management

Per the current recommendations of the World Federation of Haemophilia (WFH) guidelines for the management of haemophilia as well as of many national and international haemophilia organisations, the standard of care for all patients with severe haemophilia A is primary prophylaxis, defined as regular therapy with FVIII replacement products or other haemostasis products to prevent spontaneous bleeding. Primary prophylaxis should be initiated early in life prior to the onset of joint disease, before the second clinically evident joint bleed and before 3 years of age to prevent musculoskeletal complications from recurrent joint and muscle bleeds (Srivastava et al. 2020).

Hemlibra (emicizumab) is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

Efanesoctocog alfa (Altuvoct) is a modified recombinant factor VIII that is designed to enhance the haemostatic function. It works by binding to activated factor X (Xa) to facilitate the conversion of prothrombin to thrombin, thereby promoting the clotting cascade effectively. Its unique structure allows for stable interaction with the coagulation system, improving its efficacy in controlling bleeding.

Both Hemlibra and Altuvoct can be used in all age groups.

Another treatment option is gene therapy of haemophilia A, valoctocogene roxaparvovec (Roctavian), an adeno-associated viral serotype 5 (AAV5) vector containing a B-domain-deleted variant of human FVIII, has the potential to provide sustained FVIII activity levels. Roctavian is only indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

Episodic or on-demand FVIII treatment, i.e., treating bleeds when they occur, is no longer considered the standard of care for the management of haemophilia as it does not alter the natural history of frequent and recurrent bleeding and related complications. Patients suffering from severe haemophilia A usually receive prophylactic treatment with FVIII products, which requires regular infusion every 2 to 3 days.

2.1.2. About the product

Jivi is a recombinant B-domain deleted human coagulation FVIII variant which is site specifically conjugated with a single maleimide-derivatized 60 kDa branched PEG (two 30 kDa PEG) at the cysteine 910 (amino acid 1840 in the full length FVIII sequence), resulting in a decreased clearance and extended half-life.

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

The clinical development programme follows the relevant guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products EMA/CHMP/BPWP/144552/2009 rev 2.

September 2012 – PIP agreement

EMEA-001229-PIP01-11

April 2015 – PIP modification with EMA/PDCO

PIP modification for compliance with clinical study protocol details (resulting version: EMEA-001229-PIP01-11-M01)

January 2016 – PIP modification with EMA/PDCO

PIP modification for addition of Part 2 of the PROTECT Kids study (resulting version: EMEA-001229-PIP01-11-M02)

July 2017 – PIP modification with EMA/PDCO

PIP modification for deletion of study in PUPs from the PIP (resulting version: EMEA-001229-PIP01-11-M03).

The MAH did not seek scientific advice from the CHMP regarding the proposed extension of indication.

2.1.4. General comments on compliance with GCP

The MAH confirms that the clinical trials conducted by Bayer AG carried outside the European Union meet the Ethical requirements of Directive 2011/20/EC.

Study Number	Country
Study 21824 (Alfa-PROTECT)	Argentina
	Brazil
	Canada
	Italy
	Norway
	Turkey
	USA

No GCP deficiencies have been detected on review of the study data.

2.2. Non-clinical aspects

No new non-clinical study reports have been submitted in this application, but summaries from relevant studies were provided.

The nonclinical data for Jivi were submitted in the initial application for market authorization to the EMA and in a subsequent Type II variation to comply with a post-authorisation measure (PAM) by submitting the final study report of the chronic toxicity study including the 6 months recovery data. Since the submission of the chronic toxicity study, no new non-clinical studies for Jivi were performed.

A summary of the non-clinical literature data to support safety of pegylated products in children was provided by the MAH. Moreover, summaries of the chronic toxicity study with damoctocog alfa pegol and the juvenile toxicity studies with damoctocog alfa pegol and BAY 1025662 as well as the subacute toxicity studies with BAY 1025662 (PEG-60-linker component used in damoctog alfa pegol) were provided.

Exposure margins for children are calculated based on the highest dose of 60 IU/kg twice weekly suggested for children of 7-< 12 years of age resulting in a cumulative dose of 6240 IU/kg per year (104 doses). For patients at the age of 12 and older, the maximum recommended dose is 60 IU/kg every 5 days resulting in a cumulative dose of 4380 IU/kg per year (73 doses).

The specific activity of Jivi is 10,000 IU per mg protein. Also, damoctocog alfa pegol has a molecular weight of 234 kDa, so that the PEG-60 kDa part represents about 25.64 % of the total weight. Thus, a dose of 60 IU/kg of damoctocog alfa pegol represents a dose of about 1.54 µg/kg PEG-60 and the cumulative dose of PEG-60 per year is 160.16 µg/kg for children and 112.42 µg/kg for the older patients.

Chronic Repeat-Dose Toxicity

A chronic 26-week intravenous toxicity study with damoctocog alfa pegol was performed in male Rowett nude rats with a 13-week interim sacrifice and a 26-week post-treatment period. At start of treatment, the animals were about 8 weeks old. The rats were treated twice weekly by intravenous bolus administration at dose levels of 0, 40, 400, and 1200 IU/kg. The main groups with necropsy after 26 weeks of treatment consisted of 20 male rats, each, the interim groups with necropsy after 13 weeks of treatment consisted of 10 male rats, each, and the recovery groups treated over 26 weeks with necropsy after a 26-week treatment-free period consisted of 15 male rats, each. In addition to the standard parameters in chronic studies, also immunohistochemistry evaluation was included and toxicokinetics not only included drug substance exposure, but also exploratory PEG bioanalytical analysis in plasma and PEG cerebrospinal fluid analyses, binding anti-drug antibody parameters. Damoctocol alfa pegol was well tolerated. A transient minimal to mild decrease in mean aPTT was noted at the high dose of 1200 IU/kg in the first 3 months of treatment. Post-mortem examination did not reveal any compound-related findings. There were no signs of accumulation of PEG in the brain including choroid plexus, in kidney or spleen, as demonstrated by the lack of any positive immunoreaction to anti-PEG mAb by IHC examinations. The evaluation of the recovery animals did not show any effects up to the highest dose tested.

Mean concentrations of PEG in plasma increased with dose in the group 3 (400 IU/kg) and group 4 (1200 IU/kg containing about 40 µg/kg of PEG-60) animals after 13 and 26 weeks. No plasma concentrations (above LLOQ) of PEG were measured in the recovery period of the study. The mean plasma concentration of PEG in group 3 was 122 ng/mL (week 13) to 127 ng/mL (week 26). In group 4, concentrations were 399 ng/mL and 473 ng/mL. In group 2, 27 out of 29 samples were below LLOQ (20 ng/mL).

A positive anti-BAY 94-9027 antibody titer was only observed in one rat dose at 400 IU/kg at Week 26. All other samples were negative for anti-BAY 94-9027 antibodies.

All cerebrospinal fluid samples analyzed from all-time points were below the LLOQ (20 ng/mL) for PEG.

The no-observed-adverse-effect level (NOAEL) in the male nude rat is 1200 IU/kg twice weekly, which provides a safety margin of about 20 compared to the maximum clinical dose recommended in children at the age of 7 to 12 years (60 IU/kg twice weekly). The cumulative dose given in this study at the high dose of 1200 IU/kg is 62400 IU/kg (2 x 26 x 1200 IU/kg). That represents a total of 1040 doses of 60 IU/kg. From 7 to < 12 years of age (5 years), children may receive 520 doses (2 doses/week x 52 weeks/year x 5 years). Starting at 12 years of age, the maximum recommended dose is 60 IU/kg every 5 days, so that a patient may receive 73 doses/year (365 days/year x 1 injection / 5 days). Therefore, the total cumulative dose at the NOAEL in this study represents the cumulative dose given to patients over a period of about 12 years, when starting treatment at 7 years of age.

Juvenile Toxicity

A juvenile toxicity study was performed in Wistar rats. Two age groups were dosed each twice weekly (5 doses) intravenously (bolus) over a period of 15 days with either 0 (excipient control), 200, or 1000 IU/kg at a dosing volume of 3 mL/kg. Dosing was limited to 2 weeks to avoid the development of neutralizing antibodies to FVIII, which may reduce exposure after repeated administration. Dosing started on post-natal Day (PND) 17 (22 males) or on PND 32 (25 males). Evaluation included standard clinical endpoints, clinical pathology, immunogenicity examinations (neutralizing antibodies), and full postmortem examination including necropsy, organ weight analysis, and microscopic examination of a standard set of tissues and organs of the first 6 animals per group.

PND 17 is the earliest time point for consistent repeated i.v. administration in juvenile rats. At this age in rats, the nervous system, reproductive system, skeletal system, pulmonary system, renal development, and cardiac system as well as the hepatic system are still undergoing development and are less mature than in a child at the age of 2 years. The dosing period from PND 17 to PND 31 in rats covers the period

from infant (less than 2 years of age) to early childhood in humans, and the dosing period from PND 32 to PND 46 in rats covers the period from early childhood to adolescence (about the age of 12 years), so that the juvenile toxicity study covered the age range of interest (7 to < 12 years of age) more than appropriately, as it covered the age range from < 2 to 12 years of age.

5 doses of damoctocog alfa pegol were tolerated without any adverse effects up to the high dose of 1000 IU/kg, which represents the NOAEL. Compared to the maximum recommended clinical dose in children, the safety margin is 17.

Other studies

The safety of the PEG component BAY 1025662 (PEG-60-Maleimide-Cysteine = PEG-60-Mal-Cys) was assessed in different studies, which were part of the initial submission. Moreover, the MAH provided a summary of new data and analyses of the safety of PEGylated biopharmaceuticals which were published since the initial marketing authorization of Jivi.

Choroid plexus accumulation and potential related adverse effects were specific concerns for long-term safety of PEGylated products in pediatric populations. [Prop-C14] BAY 1025662 showed relatively high exposure in the choroid plexus, with an elimination half-life of about 117 days.

The PEG-60 exposure in the choroid plexus resulting from the repeated dose administration of BAY 1025662 in the toxicological studies in rats and after treatment of patients with clinical doses of 60 IU/kg BAY 94-9027 were simulated applying allometric scaling. The PEG-60 concentrations in the choroid plexus of rats were estimated to 418 mg/L after intravenous administration of 11 mg/kg BAY 1025662 every second day for 4 weeks. The corresponding steady state concentrations of PEG-60 in the choroid plexus of humans were predicted to be about 0.6 mg/L after administration of therapeutic doses of 60 IU/kg damoctocog alfa pegol (assuming ca. 2 µg/kg of PE-60) every 5 days for about 4 years. Thus, the simulated choroid plexus concentrations of PEG-60 at the end of the rat toxicity study were approximately 700 times higher than the respective choroid plexus concentrations in humans at steady state, providing a considerable safety margin of exposure. During the procedure, the MAH justified adequacy of the performed allometric scaling to simulate choroid plexus concentrations of PEG-60 in humans at steady state. The MAH clarified that the tissue distribution of the 60-kDa PEG linker moiety in male Wistar rats was assessed through quantitative whole-body autoradiography (QWBA) following intravenous bolus administration of [prop-14C] BAY 1025662, which is the 60-kDa PEG linker moiety of BAY 94-9027 (PH-39641). A one-compartment model was used to estimate CL and V in the tissue. CL and V were allometrically scaled from rats to humans using a scaling exponent of 1 for volume and 0.8 for clearance. Steady-state concentrations of PEG-60 in the human choroid plexus were subsequently simulated using the same structural model as in rats, along with the allometrically scaled values for CL and V. Based on the simulation, the PEG-60 concentration in the human choroid plexus should be expected to approximately 0.6 mg/L following the administration of therapeutic doses of 60 IU/kg damoctocog alfa pegol every 5 days for about 4 years.

The MAH also referred to a juvenile toxicity study with nonacog beta pegol (Refixia) in male Sprague Dawley rats performed with treatment start on PND 21. Refixia is approved for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) and can be used for all age groups.

The animals were doses at 0, 120, 380 and 1200 IU/kg twice weekly for up to 10 weeks corresponding to nominal PEG-doses of up to 6.9 mg/kg twice weekly. Recovery phase was up to 13 weeks. The rats tolerated all doses without any adverse effects. The neurobehavioral examinations did also not reveal any findings. Cerebrospinal fluid (CSF) composition regarding transthyretin and albumin was in the expected range, so that no impact on protein synthesis in choroid plexus epithelial cells or in protein transport through choroid plexus was identified. Histopathology revealed no adverse findings related to nonacog beta pegol. PEG immunostaining was detected in the choroid plexus in the epithelium, in macrophages

and in the perivascular area. It was also found in macrophages and around vascular structures in the circumventricular organs and in pituitary. In neurons, it was limited to the cranial motor nuclei.

The PEG plasma concentrations after 10 weeks of treatment were in the range of 200 mg/L after treatment with 1200 IU/kg of nonacog beta pegol (containing 6.9 mg/kg PEG). Ctrough was 49.4 mg/L. At the low dose of 120 IU/kg of nonacog beta pegol (containing 0.69 mg/kg PEG), the initial concentration was 19.9 mg/L with a Ctrough of 5.81 mg/L. The rat trough plasma concentration at the high dose was about 9-fold higher than that in children (5.6 mg/L PEG) following prophylactic treatment with once weekly doses of 40 IU/kg nonacog beta pegol (containing 0.23 mg/kg PEG). In the choroid plexus in rats, PEG was found after 3 days at the high dose, after 2 weeks starting at the mid dose and after 4 weeks at all dose levels. After end of dosing, PEG concentration decreased but was still detectable at the end of the 13-week recovery period. At the end of the dosing period, the concentrations were 28.2 µg/g at the low dose, 99.4 µg/g at the mid dose and 243.4 µg/g at the high dose. No PEG was detected in the CSF.

The data published for nonacog beta pegol support that concentrations of 243.4 µg/g tissue in the choroid plexus do not result in any adverse neurological or neuropathological effects and did also not affect the function of the choroid plexus. Like BAY 1025662 (PEG-60 moiety of damoctogoc alfa pegol), PEG-40 derived from nanocog beta pegol did not penetrate the blood-brain barrier, as it was not found in brain parenchyma. In addition, it was not found in the CSF. During the procedure, the MAH was asked to justify that the results reported for PEG-40 can be considered relevant and applicable to PEG-60. The MAH clarified that the tissue distribution, excretion and pharmacokinetics of 40 kDa PEG was examined as component of turoctocog alpha pegol (N8-GP) and the tissue distribution, excretion and pharmacokinetics of 60 kDa PEG was examined with 14C labelled BAY 1025662, which consisted of the PEG moiety and the linker used in damoctocog alfa pegol. It was shown that excretion of radioactive PEG-40 within 12 weeks post-dose was between 88 and 93% with urinary excretion and excretion via feces was ~ 10% for all doses. For PEG-60, 30.4% of the administered radioactivity was excreted, predominantly via urine (23.7%) and to a lesser extent in feces (6.3%). After 24 weeks, about 79.1% of the administered radioactivity was eliminated (64% via urine, 13.8% via feces and 0.4% recovered in the cage wash). Based on this data, it can be agreed that a PK characteristics is comparable between PEG-40 and PEG-60 labelled coagulation factors, but PEG size has an impact on clearance with total clearance decreasing with increasing PEG size. However, it is agreed that also the administered dose has an impact on the tissue concentrations.

In the chronic toxicology studies in rats, with no adverse effects and no positive immunohistochemistry in the choroid plexus observed after administration of a recombinant factor VIII PEGylated with PEG-40 (turoctocog alfa pegol) and PEG-60 (damoctocog alfa pegol) administered with about the same amounts of PEG-40 or PEG-60 over 26 weeks.

2.2.1. Ecotoxicity/environmental risk assessment

Jivi is a recombinant replacement protein of the naturally occurring coagulation factor VIII. It is catabolised during human metabolism and no active molecule is excreted by the patient. In accordance with the guideline CHMP/SWP/4447/00 (1), Jivi as a protein is exempted from an environmental risk assessment since proteins are unlikely to result in a significant risk to the environment.

2.2.2. Discussion on non-clinical aspects

No new non-clinical studies have been submitted by the MAH. Instead, a summary of non-clinical literature data to support safety of pegylated products in children was provided by the MAH. Moreover, summaries of the chronic toxicity study with damoctocog alfa pegol and the juvenile toxicity studies with damoctocog alfa pegol and BAY 1025662 as well as the subacute toxicity studies with BAY 1025662 (PEG-60-linker component used in damoctog alfa pegol) were provided. No new nonclinical issues have been identified.

2.2.3. Conclusion on the non-clinical aspects

No new non-clinical studies have been submitted to support this application. However, the MAH refers to new published data and this is considered acceptable. There are no changes for the non-clinical part of the product information.

Based on the updated data submitted in this application, the new/extended indication does not lead to a significant increase in environmental exposure further to the use of active substance. Considering the above data, Damoctocog alfa pegol is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

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

- Tabular overview of clinical studies

Study ID (Study no. / Report no.) Status	Study Objective	Intervention	Study duration	No. patients included [a]
Alfa-PROTECT [b] (21824 / B002892) Part A: Completed Part B: Ongoing	To assess safety and tolerability of Jivi replacement therapy in previously treated patients 7 to <12 years of age with severe hemophilia A	IV prophylaxis 2x/week, with a dose of 40 IU/kg (up to 60 IU/kg at investigator's discretion)	Part A: 6 months, ≥50 EDs Part B: ~18 months	Part A SAF: 35 EFF: 32
PROTECT Kids main (15912 / PH-38440) Completed	To evaluate the PK, safety, and efficacy of Jivi for prophylaxis and treatment of bleeding in previously treated children (age <12 years) with severe hemophilia A	IV prophylaxis 25-60 IU/kg twice weekly, 45-60 IU/kg every 5 days, or 60 IU/kg every 7 days at investigator's discretion.	6 months, ≥50 EDs	All: 61 ≥7 yoa: SAF: 25 EFF: 25
PROTECT Kids extension (PH-40455) Completed	To assess long-term safety and efficacy of Jivi over ≥100 EDs	As in the main study with possible adjustments based on clinical needs	≥50 EDs	All: 59 5-year completers [c] SAF: 39 ITT: 39
PROTECT VIII extension (13024 / PH-40454) [d] Extension: completed	To assess the long-term safety and efficacy of Jivi over ≥100 EDs	IV prophylaxis 30-40 IU/kg twice weekly; 45-60 IU/kg every 5 days, or 60 IU/kg every 7 days at the investigator's discretion	Extension: ≥6 months, ≥100 EDs	All: 121 5-years completers [d] SAF: 36 ITT: 36

EDs = exposure days, EFF = efficacy analysis set, ITT = intent-to-treat analysis set, IU = international units, IV = intravenous, no. = number, SAF = safety analysis set, PK = pharmacokinetics, yoa = years of age

2.3.2. Pharmacokinetics

Details of the PK data from the PROTECT Kids study were used to summarize the PK parameters for the age categories of <7 years and 7 to <12 years. The geometric mean AUC was 2840 IU*h/dL, C_{max} was 127 IU/dL, and $t_{1/2}$ was 15.6 hours. The geometric mean AUC values were ~50% lower and the Cmax was only slightly lower in the <7 years group compared to the 7 to <12 years group. The t1/2 was slightly longer in the 7 to <12 years group (15.6 h) compared to the <7 year group (13.9 h).

Table 1 Pharmacokinetic parameters (Geometric mean (%CV) and Arithmetic Mean (±SD)) for BAY 94-9027 in children <7 years and between 7-<12 years following a 60 IU/kg dose (plasma concentrations measured using chromogenic assay)

Parameters	<7 years N=16	7-<12 years N=12
AUC (IU*h/dL)	1850 (72.3)	2840 (20.3)
	2120 ± 860	2890 ± 547
C_{max} (IU/dL)	112 (27.5)[a]	127 (19.9)[b]
	116 ± 26.2	130 ± 25.0
$t_{½}$ (h)	13.9 (33.1)	15.6 (23.5)[c]
	14.5 ± 4.37	16.0 ± 3.61
MRT_{IV} (h)	18.9 (34.8)	23.5 (24.4)
	19.8 ± 5.98	24.1 ± 5.97
CL (dL/h/kg)	0.0326 (73.0)	0.0210 (19.6)
	0.0443 ± 0.0560	0.0214 ± 0.00432
V_{ss} (dL/kg)	0.616 (41.2)	0.495 (20.2)
	0.676 ± 0.393	0.505 ± 0.0989

AUC = area under the curve, C_{max} = peak plasma concentration, CL = total drug clearance from plasma, CV = coefficient of variation, MRT = mean residence time by intravenous injection, SD = standard deviation, $t_{1/2}$ = half-life, V_{ss} = volume of distribution under steady state conditions

Values have been rounded to 3 significant digits

a N=17

b N=13

c N=14

Source : Table 6–1

PK parameters based on a population PK model

The original submission included a report describing the population PK model developed from data collected in Studies 13401, 13024 and 15912. Using the information from this model and report, the MAH provided the predicted PK parameters for children aged 7 to <12 years, in addition to the age categories for patients 12 years and older. The t1/2 is lower for children aged 7-<12 years in comparison to those >12 year old (15.0 h vs 16.8h).

Table 2 PK parameters (geometric mean (%CV) based on population PK estimates, using chromogenic assay

Parameters	7 to < 12 years N=25	12 - <18 years N=12	≥ 18 years N=133	All ≥ 12 years N=145
AUC (IU.h/dL)	2694 (23)	3441 (34.2)	4052 (31.1)	3997 (31.6)
AUC_{norm} (kg.h/dL)	44.9 (23)	57.4 (32.6)	67.5 (30.6)	66.6 (31.0)
$t_{1/2}$ (h)	15.0 (19.3)	16.8 (25.2)	17.4 (28.8)	17.4 (28.4)
V_{ss} (dL/kg)	0.481 (15.3)	0.423 (15.5)	0.373 (15.6)	0.376 (15.9)
CL (dL/h/kg)	0.0223 (22.9)	0.0174 (34.2)	0.0148 (31.1)	0.0150 (31.6)

AUC = area under the curve, CL = total drug clearance from plasma, $t_{1/2}$ = half-life, V_{ss} = volume of distribution under steady state conditions

Table 3 Summary statistics for pharmacokinetic parameters of BAY 94-9027 in PLASMA based on CHROMOGENIC ASSAY (NONCOMPARTMENTAL) (PK set, excluding 2 patients)

Parameter	Age	n	Geom Mean	Geom SD	Geom CV (%)	Arithm Mean	Arithm SD	Arithm CV (%)	Min	Median	Max
AUC (h*IU/dL)	< 7 years	16	1853.68	1.91	72.26	2121.86	859.69	40.52	243.2	2115.55	3485.9
	7 -< 12 years	12	2841.93	1.22	20.31	2892.85	546.83	18.90	1923.5	2973.17	3562.3
	All ages	28	2226.22	1.72	58.72	2452.28	826.67	33.71	243.2	2571.78	3562.3
AUC_{norm} (h*kg/dL)	< 7 years	16	30.6862	1.9223	73.00	35.2292	14.4892	41.13	4.027	35.8598	57.675
	7 -< 12 years	12	47.4549	1.2142	19.59	48.2543	8.9228	18.49	33.534	49.5637	59.371
	All ages	28	36.9903	1.7307	59.25	40.8114	13.8620	33.97	4.027	42.1412	59.371
$AUC_{(0\text{-tlast})}$ (h*IU/dL)	< 7 years	16	1759.69	1.91	72.34	2011.48	798.73	39.71	226.3	2029.45	3097.9
	7 -< 12 years	12	2689.01	1.20	18.43	2728.99	472.15	17.30	1898.0	2844.89	3202.2
	All ages	28	2110.38	1.72	58.36	2318.98	758.94	32.73	226.3	2423.22	3202.2
$AUC_{(0\text{-tlast})norm}$ (h*kg/dL)	< 7 years	16	29.1302	1.9235	73.08	33.3987	13.4850	40.38	3.746	34.4057	51.255
	7 -< 12 years	12	44.9014	1.1921	17.71	45.5235	7.6695	16.85	33.090	46.9217	53.371
	All ages	28	35.0654	1.7259	58.90	38.5950	12.7407	33.01	3.746	40.1220	53.371
CL (dL/h/kg)	< 7 years	16	0.032588	1.922334	73.00	0.044259	0.056041	126.62	0.01734	0.027923	0.24835
	7 -< 12 years	12	0.021073	1.214194	19.59	0.021449	0.004328	20.18	0.01684	0.020308	0.02982
	All ages	28	0.027034	1.730734	59.25	0.034483	0.043411	125.89	0.01684	0.023768	0.24835
CL (mL/h/kg)	< 7 years	16	3.2588	1.9223	73.00	4.4259	5.6041	126.62	1.734	2.7923	24.835
	7 -< 12 years	12	2.1073	1.2142	19.59	2.1449	0.4328	20.18	1.684	2.0308	2.982
	All ages	28	2.7034	1.7307	59.25	3.4483	4.3411	125.89	1.684	2.3768	24.835
CL (mL/h)	< 7 years	16	53.424	1.885	70.31	70.347	82.487	117.26	23.41	48.902	370.04
	7 -< 12 years	12	71.381	1.348	30.56	74.361	22.365	30.08	42.11	65.803	115.40
	All ages	28	60.489	1.699	56.95	72.067	63.150	87.63	23.41	56.049	370.04
C_{max} (IU/dL)	< 7 years	17	112.317	1.310	27.48	115.750	26.239	22.67	50.14	117.544	155.45
	7 -< 12 years	13	127.523	1.217	19.86	129.787	25.047	19.30	92.11	130.646	173.85
	All ages	30	118.670	1.278	24.92	121.833	26.258	21.55	50.14	122.565	173.85

Parameter	Age	n	Geom Mean	Geom SD	Geom CV (%)	Arithm Mean	Arithm SD	Arithm CV (%)	Min	Median	Max
$C_{maxnorm}$ (kg/dL)	< 7 years	17	1.86007	1.31649	28.02	1.91955	0.44770	23.32	0.8301	2.00406	2.5538
	7 -< 12 years	13	2.14353	1.20005	18.39	2.17637	0.39266	18.04	1.5352	2.12848	2.8975
	All ages	30	1.97798	1.27909	24.99	2.03084	0.43719	21.53	0.8301	2.06751	2.8975
MRT_{IV} (HOURS)	< 7 years	16	18.8914	1.4018	34.77	19.8360	5.9802	30.15	8.161	20.5916	31.797
	7 -< 12 years	12	23.5173	1.2724	24.44	24.1573	5.9660	24.70	15.609	24.5889	37.876
	All ages	28	20.7506	1.3702	32.30	21.6880	6.2539	28.84	8.161	20.9858	37.876
$t_{1/2}$ (HOURS)	< 7 years	16	13.8988	1.3806	33.11	14.5544	4.3699	30.02	6.837	14.9594	22.847
	7 -< 12 years	14	15.6213	1.2612	23.53	16.0084	3.6106	22.55	11.040	15.8183	22.505
	All ages	30	14.6776	1.3303	29.13	15.2329	4.0330	26.48	6.837	15.5943	22.847
V_{SS} (dL/kg)	< 7 years	16	0.61563	1.48612	41.22	0.67611	0.39266	58.08	0.4445	0.54566	2.0269
	7 -< 12 years	12	0.49557	1.22095	20.16	0.50458	0.09895	19.61	0.3590	0.48404	0.6546
	All ages	28	0.56097	1.40449	34.97	0.60260	0.31164	51.72	0.3590	0.52185	2.0269
V_{SS} (mL/kg)	< 7 years	16	61.563	1.486	41.22	67.611	39.266	58.08	44.45	54.566	202.69
	7 -< 12 years	12	49.557	1.221	20.16	50.458	9.895	19.61	35.90	48.404	65.46
	All ages	28	56.097	1.404	34.97	60.260	31.164	51.72	35.90	52.185	202.69

2.3.3. Pharmacodynamics

No new PD studies have been submitted.

2.3.4. Discussion on clinical pharmacology

The MAH provided the predicted PK parameters for children aged 7 to <12 years based on the population PK model developed for the initial submission. The t1/2 is lower for children aged 7-<12 years in comparison to those >12-year-old (15.0 h vs 16.8h). No new PD studies have been submitted.

2.3.5. Conclusions on clinical pharmacology

There are no concerns from a clinical pharmacology perspective precluding approval of the proposed extension of indication for Jivi.

2.4. Clinical efficacy

2.4.1. Dose response study

No dedicated dose response studies have been conducted.

The MAH provided a summary of planned and actual doses and dose changes of study drug administration for prophylaxis (efficacy analysis set).

Table 4 Planned and actual dose changes for prophylaxis (efficacy analysis set)

	Prophylaxis 2x/week Study 15912 (N=10)	Prophylaxis 2x/week Study 21824 (N=32)	Prophylaxis 2x/week Total (N=42)
Planned dose at start of study medication (IU/kg)			
n	10	32	42
Mean (SD)	27.0 (4.8)	48.8 (6.8)	43.6 (11.4)
Median	25.0	50.0	45.0
Q1, Q3	25.0, 25.0	45.0, 55.0	40.0, 50.0
Min, Max	25, 40	37, 60	25, 60
Planned dose at start of study medication (IU/kg), categorized			
n	10 (100.0%)	32 (100.0%)	42 (100.0%)
<40	9 (90.0%)	1 (3.1%)	10 (23.8%)
40-<50	1 (10.0%)	13 (40.6%)	14 (33.3%)
50-<55	0	8 (25.0%)	8 (19.0%)
>=55	0	10 (31.3%)	10 (23.8%)
Actual dose at start of study medication (IU/kg)			
n	10	32	42
Mean (SD)	39.12 (18.61)	50.35 (8.12)	47.68 (12.22)
Median	32.84	50.77	49.75
Q1, Q3	22.73, 60.00	44.02, 56.19	40.82, 56.82
Min, Max	17.9, 60.0	36.1, 66.8	17.9, 66.8
Actual dose at start of study medication (IU/kg), categorized			
n	10 (100.0%)	32 (100.0%)	42 (100.0%)
<40	6 (60.0%)	3 (9.4%)	9 (21.4%)
40-<50	0	12 (37.5%)	12 (28.6%)
50-<55	0	8 (25.0%)	8 (19.0%)
>=55	4 (40.0%)	9 (28.1%)	13 (31.0%)
Patient had at least one dose change before end of analysis period			
n	10 (100.0%)	32 (100.0%)	42 (100.0%)
No	6 (60.0%)	16 (50.0%)	22 (52.4%)
Yes	4 (40.0%)	16 (50.0%)	20 (47.6%)
End dose higher (>5 IU/kg) than start dose	3 (30.0%)	14 (43.8%)	17 (40.5%)
End dose equal (differs 5 IU/kg or less) to start dose	1 (10.0%)	2 (6.3%)	3 (7.1%)
End dose lower (>5 IU/kg) than start dose	0	0	0

	Prophylaxis 2x/week Study 15912 (N=10)	Prophylaxis 2x/week Study 21824 (N=32)	Prophylaxis 2x/week Total (N=42)
Time to first change in planned dose (days)			
n	4	16	20
Mean (SD)	29.3 (21.3)	67.9 (54.5)	60.2 (51.6)
Median	28.5	52.0	50.5
Q1, Q3	16.0, 42.5	36.0, 96.5	25.5, 82.5
Min, Max	4, 56	3, 185	3, 185
Time to first increase in planned dose (days)			
n	3	16	19
Mean (SD)	29.7 (26.0)	67.9 (54.5)	61.9 (52.5)
Median	29.0	52.0	52.0
Q1, Q3	4.0, 56.0	36.0, 96.5	23.0, 88.0
Min, Max	4, 56	3, 185	3, 185
Planned dose at end of analysis period (IU/kg)			
n	10	32	42
Mean (SD)	30.0 (6.7)	54.9 (6.4)	49.0 (12.5)
Median	25.0	56.0	55.0
Q1, Q3	25.0, 35.0	50.0, 60.0	40.0, 60.0
Min, Max	25, 40	40, 60	25, 60
Planned dose at end of analysis period (IU/kg), categorized			
n	10 (100.0%)	32 (100.0%)	42 (100.0%)
<40	8 (80.0%)	0	8 (19.0%)
40-<50	2 (20.0%)	4 (12.5%)	6 (14.3%)
50-<55	0	5 (15.6%)	5 (11.9%)
>=55	0	23 (71.9%)	23 (54.8%)
Actual dose at end of analysis period (IU/kg)			
n	10	32	42
Mean (SD)	35.80 (13.99)	56.86 (7.61)	51.85 (13.01)
Median	34.60	57.09	55.59
Q1, Q3	25.00, 37.23	51.90, 61.86	47.47, 60.00
Min, Max	20.0, 60.0	36.4, 72.1	20.0, 72.1

	Prophylaxis 2x/week Study 15912 (N=10)	Prophylaxis 2x/week Study 21824 (N=32)	Prophylaxis 2x/week Total (N=42)
Actual dose at end of analysis period (IU/kg), categorized			
n	10 (100.0%)	32 (100.0%)	42 (100.0%)
<40	8 (80.0%)	1 (3.1%)	9 (21.4%)
40-<50	0	5 (15.6%)	5 (11.9%)
50-<55	0	5 (15.6%)	5 (11.9%)
>=55	2 (20.0%)	21 (65.6%)	23 (54.8%)

The approved posology of Jivi for prophylaxis in adults and adolescents 12 years of age and older is 45-60 IU/kg every 5 days. Based on patient clinical characteristics the dose can also be 60 IU/kg every 7 days or 30-40 IU/kg two times per week. The MAH proposed for children 7 to < 12 years of age for prophylaxis the dose of 40-60 IU/kg two times per week and a recommended starting dose of 60 IU/kg two times per week.

The proposed posology is based on the results of the integrated analysis of efficacy and safety which included two studies – a study 21824 and a study 15912. However, the recommendation for the starting dose of 60 IU/kg twice per week was mainly based on clinical data from study 21824. In this study, 71.9% of patients (23 subjects) were treated with ≥55 IU/kg, with 15 receiving 60 IU/kg. In total 42 subjects who have been administered the product 2x/week were included in the efficacy analysis set. In the pivotal study 28.1% of subjects (9 subjects in total) had an actual dose at start of study medication >=55 IU/kg administered. 37.5% and 25% of subjects used at start of study doses of 40-<50 IU/kg and

50-<55 IU/kg. However, at the end of the analysis period, the dose of >=55 IU/kg was used in 65.6% of subjects in the pivotal study. Only one subject was using actual dose <40 IU/kg.

Due to relative higher distribution volume in relation to body weight (due to lower fat content), children require higher dosages. Based on the ABR results, efficacy was better in the higher dose range. Moreover, a lower recovery at the beginning of treatment, in some patients related to transient low-titer anti-PEG IgM antibodies, and increase over time, together with the observation of better outcomes with the proposed starting dose and a frequent clinical routine to select low dosages, support the recommendation of a starting dose of 60 IU/kg.

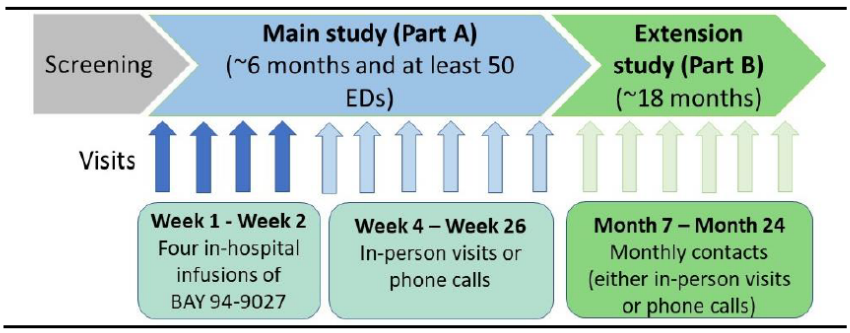
2.4.2. Main study - BAY 94-9027 / 21824

A Phase 3, single-group treatment, open-label, study to evaluate the safety of BAY 94-9027 infusions for prophylaxis and treatment of bleeding in previously treated children aged 7 to <12 years with severe haemophilia A.

Methods

Study 21824 is an ongoing open-label, single-group, uncontrolled, prospective, multicenter study which evaluates the safety of Jivi in children aged 7 to <12 years with severe haemophilia A. The main study (Part A) lasted 6 months with a visit frequency of 2x/ week for the first 4 exposure days (EDs), and monthly thereafter, and the extension study (Part B) will extend for 18 months. In Part A, participants received Jivi intravenously as prophylactic treatment 2x/week, with a dose of 40 IU/kg (up to 60 IU/kg at the investigator' s discretion). In Part B, participants may continue the same regimen or have it adjusted to 60 IU/kg IV every 5 days, at the investigator's discretion.

Figure 1 Study schema



The study was conducted at 17 study centers in 7 countries (Argentina, Brazil, Canada, Italy, Norway, Turkey, and Unites States). 40 participants were enrolled and screened, of which 35 participants received treatment and 32 participants completed Part A.

Study participants

This study enrolled male participants aged 7 to <12 years with known medical history of severe haemophilia A, and previously treated with a FVIII concentrate(s) (plasma derived or recombinant) for a minimum of 50 EDs at the time of signing the informed consent. Patients with a history or current evidence of FVIII inhibitors or any other bleeding disorder were excluded. Children who participated in the PROTECT Kids study could not be enrolled.

Treatments

Participants received Jivi IV as prophylactic treatment 2x/week, with a dose of 40 IU/kg up to 60 IU/kg at the investigator's discretion.

Objectives/outcomes/endpoints

Objectives	Endpoints
Primary objective	
Safety	
To assess safety and tolerability of Jivi replacement therapy in previously treated patients 7 to <12 years of age with severe hemophilia A	**Primary endpoint** • AESI (hypersensitivity and LoE[a]) associated with the first 4 EDs leading to discontinuation **Secondary endpoints** • Adverse drug reactions (ADRs) • Anti-drug antibody (ADA) development • Inhibitor development
Secondary objective	
To describe clinical efficacy of Jivi	**Secondary endpoints** • Annualized bleeding rate (ABR) • Jivi consumption • Number of infusions/month and year (Annualized Infusion Rate)
Other	
To further investigate long-term safety	• Quantitative PEG measurement • Renal safety-related urine and serum biomarkers • Liver enzymes • Neurological assessment
To assess the impact of Jivi in Health-related QoL	Patient-reported outcomes (PROs) questionnaires
To further investigate the study intervention and similar drugs (e.g., mode-of-action-related effects, safety) and to further investigate pathomechanisms deemed relevant to hemophilia and associated health problems	Various biomarkers (e.g., diagnostic, safety, pharmacodynamic, monitoring, or potentially predictive biomarkers)

Estimands:

The estimand for the primary objective assessed the proportion of individuals with AESIs (hypersensitivity and loss of efficacy, LoE) during the first 4 EDs of Jivi treatment and leading to discontinuation of Jivi treatment in PTPs, 7 to <12 years of age with severe haemophilia A and without inhibitors to FVIII, who did not discontinue the study for other reasons than an AESI before the fourth ED with or without emergency use of other FVIII medication.

The estimand for the secondary endpoints of the primary objective assessed the proportions of ADRs, ADA development, and inhibitor development in previously treated males 7 to <12 years of age with severe haemophilia A without prior inhibitors to FVIII who were on prophylaxis treatment with Jivi.

The estimand for the secondary objective assessed the ABR of previously treated males 7 to <12 years of age with severe haemophilia A without inhibitors to FVIII or neutralizing ADAs, who were on continuous prophylaxis treatment with Jivi for at least 3 months without major surgery and regardless of emergency use of other FVIII medication.

Sample size

The selection of the sample size of 30 is based on the assumption that less than 5% of participant out of 30 will experience an AESI and that the data will be pooled with 25 participants from the age group of 7 to <12 years of study 15192 (PROTECT KIDS) for analysis of the incidence of AESIs. Additional participants may be enrolled in the event of treatment discontinuation during the first 4 EDs of Part A for reasons other than AESI. A Bayesian beta-binomial model with each participant having an AESI as a Bernoulli response and a neutral prior probability distribution Beta (1/4,1/4) is used. The choice of the neutral prior Beta (1/4,1/4) is to avoid over influence of the prior and limit the degree of polarization of the prior toward 0 and 1. Under these assumptions, the posterior probability that the true incidence for an AESI is <5% will be > 90%.

Randomisation

The study was non-randomized.

Blinding (masking)

This was an open-label study.

Statistical methods

The study was not designed to test any predefined hypothesis. Therefore, endpoints are analysed by descriptive statistical methods. Additionally, the posterior probability that the true incidence of an adverse event of special interest (AESI) is <5% was estimated using a Bayesian approach including information from the PROTECT Kids study.

Results

Participant flow

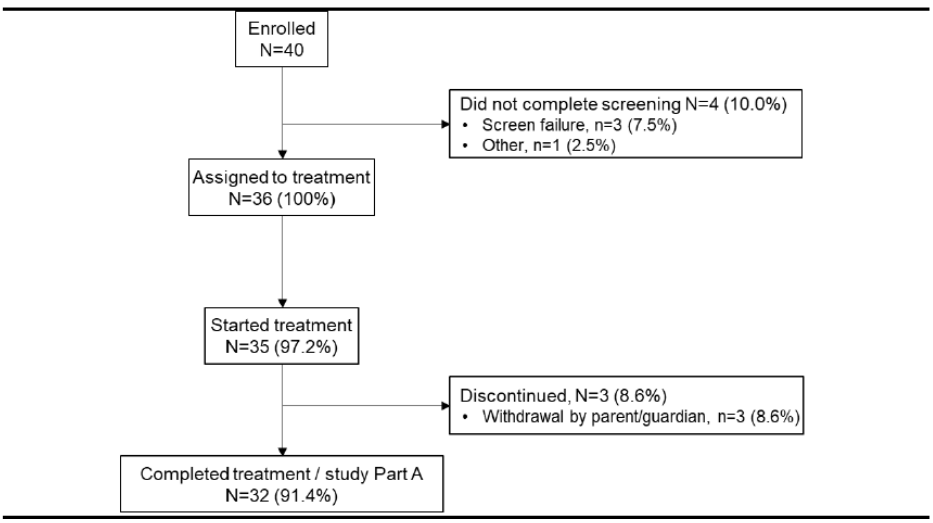


Figure 2 participant flow

Recruitment

Overall, 40 participants were enrolled and screened at 17 study centers in 7 countries. Of these, 36 participants successfully completed screening and were assigned for study intervention. 35 participants received treatment. One participant was assigned to treatment but did not receive study intervention.

Of the 35 participants who started treatment, 3 discontinued from the study after 1 ED (1 participant) and 7 EDs (2 participants) due to withdrawal by parent or guardian.

Conduct of the study

Protocol amendments

The first amendment introduced an additional year of prophylactic treatment with Jivi culminating in a total of 2 years treatment duration in children of 7 to <12 years of age. This prolongation provides long-term safety data. Furthermore, the treatment prolongation offers sustained study drug provision for 2 years and avoids unnecessary switches of responder patients to other approved FVIII products.

To better monitor study participants concerning the expected FVIII levels, the second protocol amendment recommended routine local FVIII recovery measurements to be performed at the clinical site for the first 4 EDs. This approach enabled the treating clinician to adjust the dose and/or dosing interval for the subsequent EDs if needed.

Protocol deviations

A total of 31 times schedule deviations occurred in 16 patients. These deviations were categorized as follows:

1. **Visit window deviations:** 6 patients had 1 deviation each, all related to the time between screening and baseline visit.

2. **Wash-out period for anti-drug antibody testing:** 6 deviations occurred in 5 patients, where the wash-out period after the previous infusion (at least 48 hrs) was not adhered to for blood sampling.

3. **Wash-out period for inhibitor testing:** 6 deviations occurred in the same 5 patients and visits as for point 2.

4. **Wash-out period for pre-infusion FVIII level:** 4 deviations occurred in 4 patients, who were a subgroup of patients and visits mentioned in points 2 and 3.

5. **Sampling time for post-infusion FVIII level:** 8 deviations occurred in 5 patients, where sampling time was not within 15-30 minutes after infusion

6. **Delayed informed consent form signature:** One patient had a delayed ICF signature by their mother.

The majority of these deviations occurred only at single visits. Baseline visit window deviations do not impact any results. Wash-out periods of less than 48 hours do not affect the results of ADA and inhibitor testing, but could result in a higher pre-infusion FVIII level.

Nevertheless, this result does not impact the calculation of recovery, as the pre-infusion FVIII level is taken into account. Higher pre-infusion levels may increase the mean of trough level calculation, which was not calculated in this study.

Post-infusion FVIII level measurements were scheduled at 5 visits. Sampling was to be done 15-30 minutes after the infusion. Deviations from the post-infusion sampling time included periods shorter than 15 minutes in 6 cases and one case of 35 minutes. These deviations occurred mainly during one visit per

patient, with 3 samples during Visit 2, 2 samples during Visit 3, one sample during Visit 4, and 2 samples during Visit 11. This deviation may lead to a lower FVIII peak level after infusion and therefore, to a lower recovery. Only one patient Visits 2, 3, and 11) presented 3 time points with this deviation, which may have impacted the FVIII levels post-infusion, resulting in lower recoveries.

Table 5 Number of participants with important protocol deviations (all participants enrolled)

Protocol deviation category	N=40 (100%)
Participants with any important deviation	22 (55.0%)
EXCLUDED CONCOMITANT MEDICATION TREATMENT	2 (5.0%)
PROCEDURE DEVIATIONS	7 (17.5%)
TIME SCHEDULE DEVIATIONS	16 (40.0%)
TREATMENT DEVIATIONS	4 (10.0%)

Baseline data

No relevant differences in demographics and other baseline characteristics were observed between the analysis sets.

All participants in the SAF were white with a median age of 8 years (range: 7 to 11 years), with a good balance of participants in the 7 to <9 years and 9 to <12 years age groups. The median baseline weight, height, and BMI were 31.40 kg, 137.00 cm, and 17.30 kg/m2, and are considered representative of this population.

Table 6 Demographics (SAF and mITT)

	SAF (N=35)	mITT (N=32)
Sex		
n	35 (100.0%)	32 (100.0%)
Male	35 (100.0%)	32 (100.0%)
Race		
n	35 (100.0%)	32 (100.0%)
WHITE	33 (94.3%)	31 (96.9%)
NOT REPORTED	2 (5.7%)	1 (3.1%)
Ethnicity		
n	35 (100.0%)	32 (100.0%)
NOT HISPANIC OR LATINO	16 (45.7%)	14 (43.8%)
HISPANIC OR LATINO	17 (48.6%)	17 (53.1%)
NOT REPORTED	2 (5.7%)	1 (3.1%)
Age (years)		
n	35	32
Mean (SD)	8.63 (1.37)	8.59 (1.36)
Median	8.00	8.00
Min, Max	7.0, 11.0	7.0, 11.0

Age group		
n	35 (100.0%)	32 (100.0%)
7 to <9 years	20 (57.1%)	19 (59.4%)
9 to <12 years	15 (42.9%)	13 (40.6%)
Baseline Weight (kg)		
n	35	32
Mean (SD)	34.42 (9.33)	34.54 (9.69)
Median	31.40	31.20
Min, Max	23.5, 56.1	23.5, 56.1
Baseline Height (cm)		
n	35	32
Mean (SD)	137.08 (8.49)	136.81 (8.71)
Median	137.00	136.00
Min, Max	123.0, 155.0	123.0, 155.0
Baseline Body Mass Index (kg/m^2)		
n	35	32
Mean (SD)	18.08 (3.43)	18.20 (3.56)
Median	17.30	17.35
Min, Max	14.0, 26.6	14.0, 26.6

Baseline disease characteristics

Disease characteristics were considered representative of young patients suffering from severe haemophilia A and did not differ between the analysis sets. Information regarding the FVIII gene mutation was not available (42.9%) or not applicable (20.0%) for most participants. The most frequently reported FVIII gene mutation was Intron 22 inversion (11.4%). The mean (SD) concentration of the von Willebrand Factor in plasma (calculated) was 85.0% (28.2) in the SAF. 32 of 35 participants had received prophylaxis treatment for haemophilia A prior first study treatment. A target joint was present in 5 (14.3%) of the participants at time of enrollment. The mean (SD) number of bleeds in the previous 12 months before screening was 3.11 (5.36). The mean (SD) number of joint bleeds in the same reporting period was 1.69 (3.12). For one patient, the level of factor VIII at the time of diagnosis was incorrectly documented. This was corrected after database closure.

Table 7 Baseline disease characteristics (SAF and mITT)

	SAF (N=35)	mITT (N=32)
Target Joint Present		
n	35 (100.0%)	32 (100.0%)
NO	30 (85.7%)	27 (84.4%)
YES	5 (14.3%)	5 (15.6%)
Number of target joints		
n	35 (100.0%)	32 (100.0%)
0	30 (85.7%)	27 (84.4%)
1	4 (11.4%)	4 (12.5%)
2	1 (2.9%)	1 (3.1%)
Number of target joints per participant		
n	35	32
Mean (SD)	0.2 (0.5)	0.2 (0.5)
Median	0.0	0.0
Q1, Q3	0.0, 0.0	0.0, 0.0
Min, Max	0, 2	0, 2
Participant History of Inhibitor		
n	35 (100.0%)	32 (100.0%)
NO	34 (97.1%)	31 (96.9%)
YES	1 (2.9%)	1 (3.1%)
Family History of Hemophilia		
n	35 (100.0%)	32 (100.0%)
NO	16 (45.7%)	15 (46.9%)
YES	19 (54.3%)	17 (53.1%)
Family History of Inhibitors		
n	35 (100.0%)	32 (100.0%)
NO	22 (62.9%)	20 (62.5%)
YES	2 (5.7%)	2 (6.3%)
UNKNOWN	11 (31.4%)	10 (31.3%)
Number of bleeds in reporting period[a]		
n	35	32
Mean (SD)	3.1 (5.4)	3.3 (5.6)
Median	1.000	1.000
Q1, Q3	0.000, 3.000	0.000, 3.000
Min, Max	0.00, 25.00	0.00, 25.00
No. of joint bleeds in reporting period[a]		
n	35	32
Mean (SD)	1.686 (3.123)	1.781 (3.240)
Median	0.000	0.500
Q1, Q3	0.000, 2.000	0.000, 1.500
Min, Max	0.00, 12.00	0.00, 12.00
von Willebrand Factor antigen (%) in plasma[b]		
N	35	32
Mean (SD)	85.0 (28.2)	87.2 (28.4)
Median	77.0	77.5
Q1, Q3	64.0, 108.0	68.0, 110.0
Min, Max	47, 151	47, 151

Prior and concomitant therapy

Prior FVIII therapy

Per protocol, all participants had received prior therapy for FVIII deficiency for at least 50 EDs prior to study entry. The median age at first treatment was 12.0 months. For 15 (42.9%) patients, the type of first treatment regimen was regular prophylaxis. The majority (91.4%) were on a prior prophylactic treatment regimen when entering the study.

Other relevant prior medications

A total of 17 participants had received Covid-19 vaccination prior to enrolment. Two of these participants presented low-titer anti-PEG antibodies before study treatment.

Table 8 Prior hemophilia treatment (SAF and mITT)

	SAF (N=35)	mITT (N=32)
Age at first treatment (months)		
n	35	32
Mean (SD)	12.3 (7.5)	11.9 (7.6)
Median	12.0	11.0
Q1, Q3	8.0, 16.0	8.0, 15.5
Min, Max	0, 32	0, 32
Type of First Treatment Regimen		
n	35 (100.0%)	32 (100.0%)
ON DEMAND	18 (51.4%)	17 (53.1%)
REGULAR PROPHYLAXIS	15 (42.9%)	13 (40.6%)
UNKNOWN	2 (5.7%)	2 (6.3%)
Type of First Treatment		
n	35 (100.0%)	32 (100.0%)
FACTOR VIII	2 (5.7%)	2 (6.3%)
PLASMA DERIVED FACTOR VIII	2 (5.7%)	2 (6.3%)
RECOMBINANT FACTOR VIII	31 (88.6%)	28 (87.5%)
Prior Treatment Type		
n	35 (100.0%)	32 (100.0%)
ON DEMAND	3 (8.6%)	3 (9.4%)
REGULAR PROPHYLAXIS	32 (91.4%)	29 (90.6%)
Total Number of Exposure Days		
n	35 (100.0%)	32 (100.0%)
>= 151	35 (100.0%)	32 (100.0%)
Did First Treatment Regimen Change		
n	35 (100.0%)	32 (100.0%)
NO	8 (22.9%)	7 (21.9%)
YES	27 (77.1%)	25 (78.1%)
Age at the change of first treatment (months)		
n	27	25
Mean (SD)	36.7 (26.6)	37.7 (27.4)
Median	28.0	28.0
Q1, Q3	18.0, 50.0	21.0, 50.0
Min, Max	7, 121	7, 121

Concomitant medication

Concomitant medication was any medication that the participant received within 3 months of study enrollment, was receiving at the time of study enrollment, or received during the study. The overall profile of concomitant medication usage is representative of the study population, demonstrating typical patterns within the cohort. Almost three-quarters (74.3%) of participants had prior medications (excluding FVIII treatment). Concomitant medications were used by more than half (62.9%) of participants, and more than half (60.0%) of the participants started at least one new concomitant medication during treatment period.

The most prominent concomitant medications overall were: analgesics (12 participants), nasal preparations and ophthalmologicals (11 participants each) and antibacterials for systemic use and stomatological preparations (9 participants each). Except for nasal preparations, these concomitant medications were newly started during the treatment period in all cases. Seven participants were administered new concomitant antihemorrhagic medications, with 3 of them receiving alternative FVIII products. One participant received an alternative FVIII treatment during discontinuation of study drug due to LoE. The other 2 participants each received a single treatment with an alternative FVIII product: one due to an AE (fall on pavement while running) and the other to treat a bleed during the first 4 Eds according to protocol.

During the procedure the MAH clarified that 2 patients reported single uses of tranexamic acid for treatment of an unspecified bleed. Another patient received epinephrine bitartrate as an inhalation for an adverse event of repeated sneezing and acute pharyngitis. One patient received desmopressin for 13 days due to a Medical History event of enuresis during the night.

It is agreed that the use of these antihemorrhagics is not expected to impact the study results.

Exposure and study intervention compliance

All 35 participants in the SAF received Jivi treatment, with the majority completing at least 50 EDs (n=31, 88.6%). The median number of exposure days was 53.0 (range: 1 to 59), and the median treatment duration was 182.0 days (range: 7, 198).

Numbers analysed

All treated participants (35) are included in the SAF. One participant withdrew from the study before the 4th ED and was excluded from the mSAF, resulting in 34 participants in this analysis set. The mITT includes 32 participants. 3 participants were excluded due to the absence of injection/bleeding data from the EPD, or because, despite receiving at least 1 dose of study intervention, they lacked subsequent data for infusions/bleeds documented in the EPD for at least 3 months.

Table 9 Number of participants

	Total N=35 (100%)
Participants valid for SAF	35 (100.0%)
Participants valid for mSAF	34 (97.1%)
Participants valid for ITT	34 (97.1%)
Participants valid for mITT	32 (91.4%)

Intercurrent events

Primary estimand: Out of the 35 participants who received at least 1 dose of study drug, 1 (2.9%) participant had the intercurrent event treatment discontinuation for any reason other than AESI before the fourth ED. This participant was not included in the assessment of the primary endpoint and was excluded from the mSAF. Two participants reported emergency use of other FVIII products during the first four EDs of the study; however, their data was included in the analysis according to the treatment policy strategy.

Secondary estimands: Out of the 35 participants who received at least 1 dose of study drug, 3 (8.6%) had the intercurrent events treatment discontinuation for any reason before month 3. These patients were excluded from the mITT. No participant reported development of an inhibitory antibody to FVIII. An AESI of LoE was reported for 1 participant, who discontinued and then restarted study drug after disappearance of anti-PEG antibodies. Therefore, this participant was included in the mITT.

For the intercurrent events treatment discontinuation for any reason after month 3 and emergency use of other FVIII medication, no participants discontinued treatment after month 3 for any reason, and data from participants who received other FVIII during the study were included in the analysis according to the treatment policy strategy. No emergency major surgery was reported during Part A of the study.

Outcomes and estimation

Annualised bleeding rate

Throughout the study, 16 (50%) participants did not present any bleeds, treated or untreated. The remaining 50% reported a total of 64 bleeds, with the majority being spontaneous (46/64) and 46.9 % being skin/mucosa bleeds. Out of 32 participants, 23 (71.9%) did not experience any joint bleeds. Of the 64 reported bleeds, only 21 required treatment with most being trauma-related (11/21).

The majority of the 43 untreated bleeds were mucosa bleeds (30 bleeds). Most untreated skin/mucosa bleeds were reported by a single participant (nose bleeds), resulting in an exceptionally high ABR of 49.5 for this participant, which influenced the overall mean ABR for total bleeds.

Other untreated bleeds, mostly mild intensity, did not require an additional infusion as they occurred close to the scheduled prophylaxis infusion. ABR for treated bleeds are presented in detail below.

The median ABR (Q1, Q3) for all treated bleeds was 0 (0, 1.9). The mean (95% CI) ABR based on a negative binomial regression model is 1.33 (95% CI: 0.61, 2.90). The median ABR (Q1, Q3) for each type of treated bleed was 0 (0, 0). When including untreated bleeds, the median ABR (Q1, Q3) was 0.9 (0, 4.9).

Table 10 Summary of all bleeds (mITT)

	All bleeds (N=32)	Spontaneous bleeds (N=32)	Trauma bleeds (N=32)	Joint bleeds (N=32)
Annualized number of total bleeds				
n	32	32	32	32
Mean (SD)	4.09 (9.03)	2.94 (8.49)	1.09 (2.47)	1.15 (2.46)
Median	0.92	0.00	0.00	0.00
Q1, Q3	0.00, 4.92	0.00, 2.08	0.00, 1.87	0.00, 1.90
Min, Max	0.0, 49.5	0.0, 47.4	0.0, 12.5	0.0, 10.4
Annualized number of treated bleeds				
n	32	32	32	32
Mean (SD)	1.34 (2.65)	0.57 (1.49)	0.70 (2.01)	0.71 (1.80)
Median	0.00	0.00	0.00	0.00
Q1, Q3	0.00, 1.93	0.00, 0.00	0.00, 0.00	0.00, 0.00
Min, Max	0.0, 10.4	0.0, 6.3	0.0, 10.4	0.0, 8.3
Proportion of participants who had bleed				
n	32 (100%)	32 (100%)	32 (100%)	32 (100%)
No	16 (50%)	20 (62.5%)	23 (71.9%)	23 (71.9%)
Yes	16 (50%)	12 (37.5%)	9 (28.1%)	9 (28.1%)

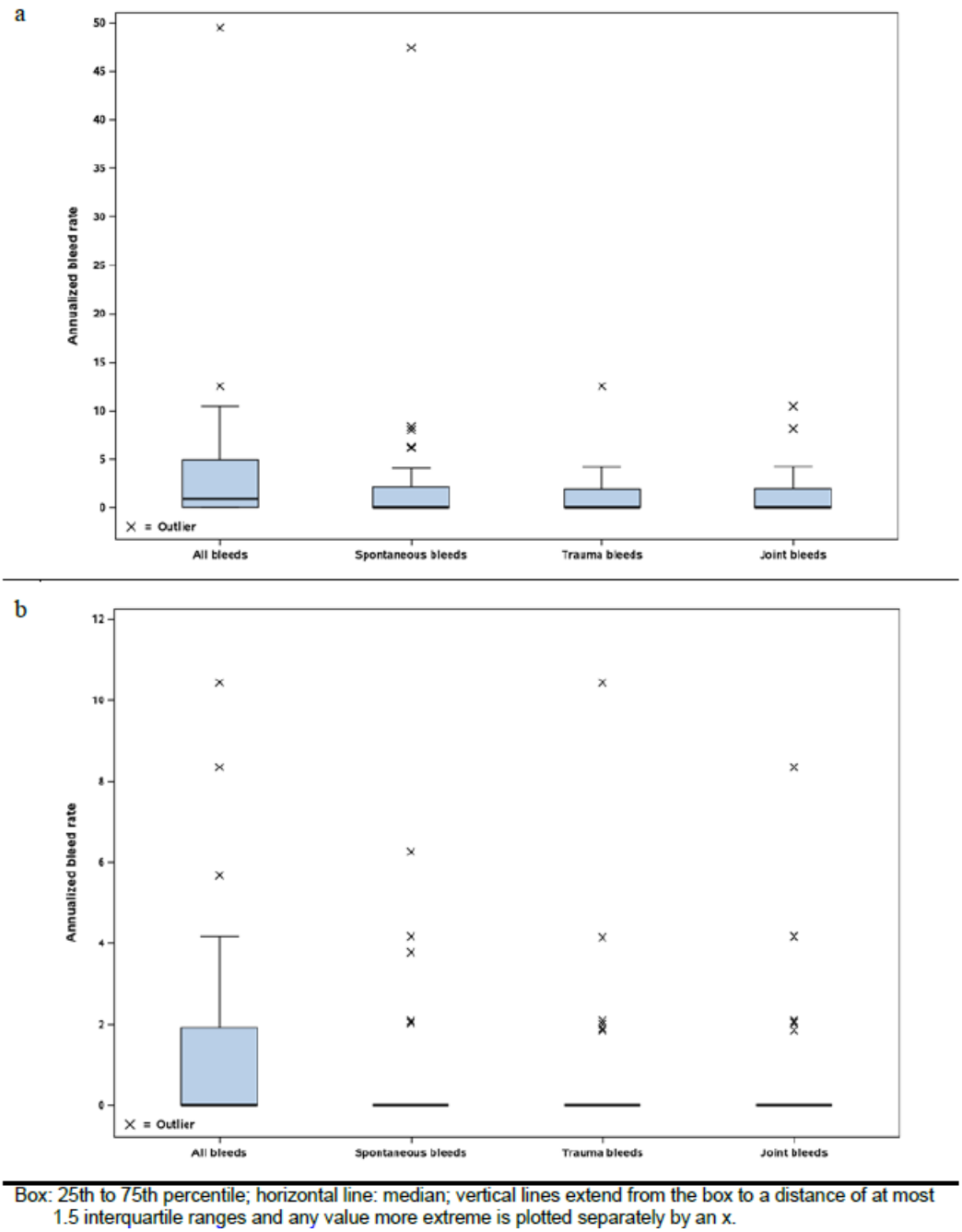


Figure 3 Annualized number of total (a) and treated (b) bleeds by category (mITT)

Summary of bleed location and severity

Almost half of the total bleeds were skin/mucosa bleeds (46.9%). All 30 skin/mucosa bleeds were untreated and the majority of them were reported by a single participant who had reported a similar frequency of nose bleeds before enrolment in the study. The participant was successfully treated by a minor surgical intervention during the study and the number of bleeds decreased substantially.

Most treated bleeds were joint bleeds (52.4%). The most common locations for joint bleeds were the foot and knee joints. Untreated joint bleeds were of mild intensity and the regular prophylaxis infusion was sufficient to control the bleed. Severe intensity was reported for 7.8% of all bleeds.

Table 11 Summary of bleed location and severity (mITT)

	Treated bleeds	Untreated bleeds	Total
Type of bleed			
n	21 (100.0%)	43 (100.0%)	64 (100.0%)
JOINT	11 (52.4%)	7 (16.3%)	18 (28.1%)
MUSCLE	3 (14.3%)	3 (7.0%)	6 (9.4%)
SKIN/MUCOSA	0	30 (69.8%)	30 (46.9%)
INTERNAL	0	1 (2.3%)	1 (1.6%)
OTHER	7 (33.3%)	3 (7.0%)	10 (15.6%)
Severity/Intensity			
n	21 (100.0%)	43 (100.0%)	64 (100.0%)
MILD	6 (28.6%)	37 (86.0%)	43 (67.2%)
MODERATE	10 (47.6%)	6 (14.0%)	16 (25.0%)
SEVERE	5 (23.8%)	0	5 (7.8%)

The total count of types of bleed may exceed 100% due to some bleeds having more than one type.
Source: Table 8.2.1 / 4

Efficacy in the treatment of bleeds – treatment attributes and response to treatment of bleeds

During the study, 64 bleeds occurred. The majority (67.2%) did not require any additional infusion and were documented as untreated bleeds, most of them were skin/mucosa bleeds, e.g. nose bleeds. Those bleeds that required a treatment (n=21) were controlled mostly with a single infusion (71.4%). Response to treatment of bleeds was rated as either good or excellent for most bleeds (71.4%).

Table 12 Treatment attributes for treated bleeds and response to treatment (mITT)

	Total
Number of infusions required to control the bleed	
n	21
Mean (SD)	1.4 (0.9)
Median	1.0
Q1, Q3	1.0, 2.0
Min, Max	1, 5
Number of infusions required to control the bleed, categorized	
n	21 (100.0%)
1 infusion	15 (71.4%)
2 infusions	5 (23.8%)
>=3 infusions	1 (4.8%)
1 or 2 infusions	20 (95.2%)
Time to first follow-up infusion (days)	
n	6
Mean (SD)	1.022 (0.777)
Median	1.074
Q1, Q3	0.542, 1.103
Min, Max	0.00, 2.34
Response to treatment	
n	21 (100.0%)
EXCELLENT	6 (28.6%)
GOOD	9 (42.9%)
MODERATE	5 (23.8%)
EXCELLENT OR GOOD	15 (71.4%)
POOR	1 (4.8%)

Source: Table 8.2.1 / 4 and Table 8.2.1 / 5

FVIII recovery

Dosing for FVIII recovery was not standardized and ranged from 40 to 60 IU/kg with a mean of 50-52 IU/kg for the first 4 infusions. The median (min, max) FVIII recovery across visits in the absence of any anti-PEG antibodies was 1.69 (1.1, 2.9) kg/dL. There was a slight variation in median recovery from baseline to end of Study Part A (Visit 11), with a slight decrease at Visit 3 (ED 2) and Visit 5 (ED 4)

primarily due to participants with positive anti-PEG antibodies. However, recovery showed an increase after 6 months.

Table 13 . FVIII recovery values by visit and across all visits(mITT)

Visit Name	n	Median	Q1, Q3	Min, Max
Baseline	31	1.70	1.41, 1.95	1.2, 3.9
Visit 3 (ED 2)	31	1.54	1.21, 1.86	0.1, 2.6
Visit 4 (ED 3)	27	1.76	1.29, 2.10	0.0, 4.8
Visit 5 (ED 4)	27	1.53	1.31, 1.90	0.1, 3.2
Visit 11 (after 6 mo)	29	2.06	1.80, 2.30	0.8, 3.6
Across all visits[a]	32	1.69	1.48, 1.97	1.1, 2.9

In participants with positive antibody measurements, recovery was within or close to the lower range observed in the absence of antibodies, except for one participant with LoE. When low-titer IgM anti-PEG antibodies were present, the recovery ranged between 0.8 and 1.8 kg/dL. In the presence of high-titer anti-PEG IgM antibodies, the recovery was 0.06 kg/dL, which increased as the antibody titer decreased and normalized after antibodies disappeared.

In children, isolated instances of low recovery have been observed without the presence of anti-PEG antibodies (Coppola et al., 2024). In samples from the Alfa-PROTECT study analyzed by the central laboratory, values <1 kg/dL were observed in 8/32 participants in the absence of anti-PEG antibodies. The lowest value recorded was 0.11 kg/dL, and one value of 0.0 may have been due to a sample handling issue. In two cases, the recovery was <0.5 kg/dL without the presence of anti-PEG antibodies or signs of LoE. In most cases, these instances of low recovery were observed only in single blood samples, mainly at the beginning of the study. A sampling problem or sample handling issue cannot be ruled out.

Patient-reported outcomes (PRO) questionnaire

Results from the Haemo-QoL questionnaire show a reduction of the overall score from baseline to Visit 11, mainly in the subscores for physical health, feelings and treatment, indicating an overall improvement in health-related quality of life.

At the end of Study Part A, both the caregivers and participants reported similar global impressions of change. Most reported an improvement (minimally, much, or very much improved), with the predominant response 'Very much improved' (11 from caregivers (34.4%) and 16 from patients (50%)). This trend is echoed by the Global Impression of Severity: Transitions from baseline to end of study. For approximately one-third of participants, an improvement was reported by caregivers and patients (13 (40.6%) and 11 (34.4%), respectively). No change in severity was reported for 12 and 18 participants (by caregivers and patients). Only for a few individuals a decline of severity was reported (7 (21.9%) and 3 (9.4%) from caregivers and patients, respectively).

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

Introduction

The MAH provided integrated efficacy analysis which included 2 studies:

- Study 21824 (Alfa-PROTECT) study in patients 7 to <12 years of age, main study (Part A) (pivotal study for this Variation application, described in details above).
- Study 15912 (PROTECT Kids) in patients <12 years of age, main study excluding patients <7 years of age

The PROTECT Kids study was an open-label, uncontrolled, multi-center Phase 3 study to assess the PK, efficacy, and safety of treatment with Jivi for prophylaxis and treatment of bleeds in previously treated children with severe haemophilia A (<12 years of age and at least 50 prior EDs with any FVIII concentrates). The study was comprised of 3 parts: main study, expansion group, and extension study. All patients completing either the main study or expansion were offered participation in the optional extension study to assess the long-term safety of Jivi over at least 100 accumulated EDs (main study + extension). Patients continued to be monitored for efficacy and safety every 6 months and at the end of the extension. The main study enrolled patients <12 years of age in 2 age subgroups (6 to <12 years and <6 years) with severe hemophilia A (FVIII <1%) and ≥50 prior EDs. Patients were treated prophylactically with Jivi on a regular schedule for a minimum of 50 EDs. Doses and dose intervals (25-60 IU/kg 2x/week, 45-60 IU/kg every 5 days, or 60 IU/kg every 7 days) were picked by the investigator based on patient characteristics and bleeding phenotype and may have been adjusted at any time as needed. Jivi was also used for treatment of any breakthrough bleeding events.

Study population and treatment duration

A total of 61 PTPs were enrolled in the main study and received treatment; 53 patients completed the main study. Of these patients, 60 were included in the primary efficacy summaries; 29 were in the 6 to <12 years age group. One patient in this age group discontinued (adverse event: hypersensitivity) during EDs 1-9 with a treatment duration of less than one month and was not included in the efficacy assessment of annualized bleed rate. Overall, the population used in the efficacy analysis included 53 patients with at least 50 EDs; 28 patients were in the 6 to <12 years group. The median duration of study treatment in the main study for the 6 to <12 years group was 245 days (range: 182 to 334). The median number of EDs was 54 (range: 51 to 63); overall, all 28 patients in this age group had at least 50 EDs and 27 continued in the extension study. All patients included were male. The median age in the 6 to <12 years group was 9 years (range: 6 to 11). Most patients were white (96.4%) and not Hispanic or Latino (100%). Baseline characteristics were considered representative of patients with severe hemophilia A. Most patients (86.2%) had received FVIII prophylaxis prior to the study. Medical history and prior medication were in line with the inclusion criteria.

Annualised bleeding rate

The 28 patients from the 6 to <12 years group had a median ABR of 2.92 (Q1, Q3: 0.0, 6.66). The median ABR for spontaneous and joint bleeds was 1.47 (Q1, Q3: 0.0, 3.03) and 0.0 (Q1, Q3: 0.0, 2.84), respectively, for patients in this age group. A total of 10 patients were treated with a twice weekly regimen, 15 patients with extended intervals of every 5 days or every 7 days, and 3 changed regimens during the 6-month study duration.

Jivi was effective for the treatment of bleeds in the 6 to <12 years group, with approximately 93% of bleeds effectively treated with 1 to 2 infusions. Bleeds were treated according to local standard of care, using a mean dose of 43.3 (±SD 11.2) IU/kg/infusion. Patient/caregiver-reported assessment of response to treatment was "excellent" or "good" in the majority (83.8%) of cases.

Comparison and analyses of results across studies

The efficacy population for the integrated analysis includes pooled results from the PROTECT Kids main study and Alfa-PROTECT Part A; the duration of each study part was approximately 6 to 8 months and ≥50 EDs. Patients included in the pool were aged 7 to <12 years, received at least 1 dose of Jivi, had diary data for at least 3 months, and did not develop an inhibitor against FVIII.

Pooled efficacy results are presented for the 2x/week prophylaxis group and the total prophylaxis group.

Study populations

The efficacy pool included 57 patients (32 from Alfa-PROTECT Part A and 25 from PROTECT KIDS main study). Among these patients, 42/57 were treated with a twice weekly regimen and 15 patients were treated either with an every 5-day (n=14) or every 7-day regimen (n=1). Extended intervals were only used in the PROTECT Kids study. Characteristics of the 2x/week and total prophylaxis groups were similar. The 2x/week group is described below.

The median treatment duration and the median time in study were both 182 days (range: 172 to 238). The median age at enrollment was 8.5 years (range: 7.0 to 11.0) and the median BMI was 17.20 kg/m^2. Baseline disease characteristics were representative of patients suffering from severe hemophilia A without history of an inhibitor to FVIII, and reflective of the age group.

Pooled efficacy results

Annualized bleeding rate

The estimated mean ABR for all treated bleeds based on a negative binomial regression model was 1.96 (95% CI: 1.01, 3.82) for the 2x/week group and 2.30 (95% CI: 1.58, 3.36) for the total prophylaxis group.

In the 2x/week group, the median (Q1; Q3) ABR for treated bleeds was 0.0 (0.0, 2.0), with corresponding median ABRs for treated spontaneous, trauma, and joint bleeds all being 0.0 (0.0, 0.0). In the total prophylaxis group, the median (Q1; Q3) ABR for treated bleeds was 0.0 (0.0, 4.2), with the corresponding median (Q1; Q3) ABRs for treated spontaneous, trauma, and joint bleeds being 0.0 (0.0, 2.0), 0.0 (0.0, 1.9), and 0.0 (0.0, 1.9), respectively.

Other efficacy results

The 42 patients in the 2x/week prophylaxis group presented a total of 36 treated bleeds. The 57 patients in the total prophylaxis group presented with a total of 84 bleeds. Joint bleeds were most common in both treatment groups (55.6% and 51.2%, respectively). The majority of bleeds in both groups was categorized as mild or moderate (83.4% and 86.9%, respectively).

In both treatment groups, most bleeds (>80%) were managed with 1 infusion, while those requiring multiple infusions had a mean time to the first follow-up infusion of approximately 1 day, with a median of 1.1 days.

For the majority of bleeds, the response to treatment was good or excellent (83.3% and 79.8% in the 2x/week and total prophylaxis groups, respectively).

Incremental recovery

FVIII activity was measured using a validated chromogenic assay at baseline and at various time points during the 6 months of treatment.

The mean recovery across all visits in the absence of any anti-PEG antibodies was 1.93 kg/dL (SD: 0.54) for the 42 patients in the 2x/week group, with a range from 1.1 to 3.8. Similarly, among the 57 patients in the total prophylaxis group, the mean recovery was 1.97 kg/dL (SD: 0.51), ranging from 1.1 to 3.8 kg/dL. Recovery was reduced in some children with low-titer anti-PEG antibodies, with the lowest observed value being 0.8 kg/dL.

Analysis of clinical information relevant to dosing recommendations

The possible dose range for the twice weekly regimen in the PROTECT Kids study was 25-60 IU/kg. Some patients started with the low dose of 25 IU/kg but increased it to 35-40 IU/kg within the first 2 months. In the Alfa-PROTECT study, the proposed dose range was 40-60 IU/kg. At the start of the study,

18 patients (56.3%) began with a dose between 50-60 IU/kg, while the remaining 14 patients started with a dose <50 IU/kg. Primarily within the first two months, 10 of these 14 patients increased their dose by >5 IU/kg, with 9 reaching a dose ≥55 IU/kg.

The integrated analysis of both studies revealed a median (Q1; Q3) dose of 52 IU/kg (39 to 59) in the 2x/week prophylaxis treatment group. This analysis supports the dosing recommendation of 40-60 IU/kg twice weekly in patients 7 to <12 years of age. Due to a lower recovery in children, mainly at the beginning of the treatment, a starting dose of 60 IU/kg is recommended.

Data from patients completing at least 5 years of treatment in the PROTECT Kids extension study further reinforced this dosing recommendation. The median dose for the twice weekly treatment group during the extension study was 37 IU/kg for the age group 6-<12 years.

Similarly, data from patients who completed at least 5 years of treatment in the PROTECT VIII extension study support dosing recommendations for patients ≥12 years of age as per SmPC.

These subgroup analyses demonstrate sustained efficacy over the long term, reinforcing the recommended dosing regimens and highlighting the long-term benefits of Jivi in maintaining hemostatic control in patients with hemophilia A.

Persistence of efficacy and/or tolerance effects

The persistence of efficacy over time is anticipated with Jivi and has been demonstrated for a treatment period of up to 7 years during the PROTECT VIII/Kids extension studies. Tolerance effects (i.e., loss of therapeutic effects over time) have not been observed.

No new analysis of clinical information relevant to persistence of efficacy and/or tolerance effects was performed during Part A of the Alfa-PROTECT study. Efficacy outcomes in the integrated analysis were consistent with the previous findings.

Supportive studies

PROTECT Kids extension study

The PROTECT Kids extension study was offered to all patients who all patients who completed the main study. The extension study was to last for a minimum of 100 cumulative EDs or until marketing authorization. The dosing regimens in the extension study were the same as in the main study and the expansion and could be adjusted to the clinical needs of each patient within a range of 25-60 IU/kg per administration.

Study population and treatment duration

In the extension study, 39/59 (66.1%) patients completed ≥5 years of treatment, including both the main and extension study periods. Results from these patients were included in the efficacy summaries.

During the extension study, the dose regimens were:

- 16 patients every 5 days (45-60 IU/kg)
- 7 patients twice a week (25-60 IU/kg)
- 4 patients every 7 days (60 IU/kg)
- 12 patients with variable frequency

Upon entering the main study, 17/39 (43.6%) patients were <6 years old and 22/39 (56.4%) patients were 6 to <12 years old. The main study had a duration of 6-8 months. By the end of the extension

study, all patients were over 7 years old, with 13 patients aged between 8 to <12 years and 26 patients aged between 12 to ≤18 years.

The median duration of the extension study was 5.4 years (range: 4.5 to 5.9). The median number of EDs was 424 (range: 260 to 612). The median treatment duration for the total time in study was 6.1 years (range: 5.2 to 6.6). The median number of EDs was 477.0 (range: 311 to 671). Most patients were white (92.3%) and not Hispanic or Latino (94.9%).

Annualised bleeding rate in extension

The 39 patients who completed 5 years of treatment had a median (Q1, Q3) ABR of 1.89 (0.71, 3.34). The median (Q1; Q3) ABR for spontaneous and joint bleeds was 0.38 (0.18, 0.88) and 0.86 (0.22, 1.75), respectively.

Other efficacy results

Jivi was effective for the treatment of bleeds, with approximately 93% of bleeds effectively treated with 1 to 2 infusions.

PROTECT VIII extension study

The PROTECT VIII extension study was offered to all who had completed Part A (prophylaxis or on-demand). The extension study was to last for a minimum of 6 months and/or at least 100 cumulative EDs or until marketing authorization.

In the extension, prophylaxis patients could either continue their regimen or had the option of switching to one of the other prophylaxis regimens. On-demand patients entering extension had the choice to continue their on-demand treatment or switch to one of the prophylaxis regimens, thus becoming prophylaxis patients.

Study population and treatment duration

In the extension study, 36/121 (29.8%) patients completed ≥5 years of treatment, including both the main and extension study periods. Results from these patients were included in the efficacy summaries.

During the extension study, the dose regimens were:

- 10 patients every 5 days (45-60 IU/kg)
- 4 patients twice a week (25-60 IU/kg)
- 8 patients every 7 days (60 IU/kg)
- 14 patients with variable frequency

Upon entering the main study, 4 patients were <18 years old. The main study had a duration of 36 weeks. By the end of the extension study, all patients were over 18 years old, with a median age of 42.5 (range: 19, 66).

The median duration of the extension study was 5.4 years (range: 4.3 to 6.3). The median number of EDs was 371.5 (range: from 244 to 621). The median duration of study treatment in all study parts was 6.2 years (range: 5.0 to 7.0). The median number of EDs was 428.5 (range: 293 to 698). All patients were white and most were not Hispanic or Latino (97.2%).

Annualized bleeding rate in extension

The 36 patients who completed 5 years of treatment had a median (Q1; Q3) ABR of 1.14 (0.43, 2.10). The median (Q1; Q3) ABR for spontaneous and joint bleeds was 0.53 (0.09, 1.41) and 0.87 (0.36, 1.70), respectively.

Other efficacy results

Jivi was effective for the treatment of bleeds, with 93.5% of bleeds effectively treated with 1 to 2 infusions.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

To support the proposed extension of the indication to PTP patients ≥7 years of age, the MAH submitted results of the pivotal study Alfa-PROTECT, an integrated analysis including results of studies Alfa-PROTECT and PROTECT KIDS (7-12 years) and long-term efficacy data collected in patients who completed at least 5 years of treatment in the PROTECT KIDS study.

The Alfa-PROTECT study is an ongoing open-label, single-group, uncontrolled, prospective, multi-centre Phase 3 study to evaluate the safety of Jivi for prophylaxis and treatment of bleeding in previously treated children aged 7 to <12 years with severe haemophilia A who had received prophylaxis treatment before the study (≥50 EDs). The Study consist of two parts (PART A – completed and PART B – ongoing). The main study (Part A) assessed the safety and efficacy of Jivi (at the dose of 40IU/kg up to 60IU/kg at the investigator's discretion) for prophylaxis and treatment of breakthrough bleeding for 6 months and at least 50 EDs. After completion of the main study, patients were offered to continue in the extension study (Part B) for additional 18 months, which will further evaluate the long-term safety, clinical efficacy, and impact of Jivi on health-related QoL. In Part B, each patient will continue their prophylaxis dose regimen from Part A or can be adjusted to 60 IU/kg every 5 days at the investigator's discretion. The proposed dosing schedule is considered justified. The primary endpoint for this study was defined as the occurrence of AESI (i.e., hypersensitivity or LoE) associated with the first 4 EDs of BAY 94-9027 treatment leading to discontinuation.

The overall design of the study is considered acceptable.

Efficacy data and additional analyses

In total 50% participants did not present any bleeds during the study. 71.9% of participants did not experience any joint bleeds. The majority of the reported bleeds (a total of 64 bleeds) were spontaneous (46/64) with 46.9 % skin/mucosa bleeds. 21 of reported 64 bleeds required treatment. 11/21 of bleeds that required treatment were trauma-related. Most treated bleeds were joint bleeds (52.4%). Severe intensity was reported for 7.8% of all bleeds and 23.8% of treated bleeds. 47.6% of the treated bleeds were of moderate severity.

Response to treatment of bleeds was rated as either good or excellent for most bleeds (71.4%). Poor response was reported in one subject. The median ABR (Q1, Q3) for all treated bleeds was 0 (0, 1.9) and the mean (95% CI) ABR based on a negative binomial regression model is 1.33 (95% CI: 0.61, 2.90). The median ABR (Q1, Q3) for each type of treated bleed was 0 (0, 0). When including untreated bleeds, the median ABR (Q1, Q3) was 0.9 (0, 4.9).

The median FVIII recovery across visits in the absence of any anti-PEG antibodies was 1.69 (1.1, 2.9) kg/dL. In the presence of high-titer anti- PEG IgM antibodies, the recovery was 0.06 kg/dL.

Analysis of the the Haemo-QoL questionnaire show generally comparable global impressions of change for both the caregivers and participants at the end of Study Part A. A reduction was shown for physical health, feelings and treatment. In Global Impression of Severity 40.6% of caregivers and 34.4% of

patients reported an improvement. However, 21.9% of caregivers and 9.4% of patients reported decline of severity.

Overall, the results of the study can be considered acceptable to support the proposed extension of the indication.

Assessment of paediatric data on clinical efficacy

The proposed extension of the indication considered paediatric population.

2.4.4. Conclusions on the clinical efficacy

The proposed extension of the indication to subjects ≥7 years of age is acceptable.

2.5. Clinical safety

Introduction

At the time of the initial submission, the indication for all pegylated FVIII/FIX products was restricted to previously treated haemophilia A patients aged 12 years and older. This restriction was due to limited information on potential safety concerns related to long-term PEG exposure in young children and the potential risk of PEG accumulation in the choroid plexus and other organs. In addition, the MAH proposed this age restriction due to an observed immune response to the PEG component of Jivi in children <6 years of age. This response included hypersensitivity and/or loss of efficacy (LoE) due to the development of anti-PEG IgM antibodies within the first 4 EDs. The exclusion of the age group 6-<12 years was proposed as a safety measure, given the small number of patients studied in this age group. This concern was subsequently addressed in a new safety study, Alfa-PROTECT (BAY 94-9027 / 21824), in the age group 7-<12 years. Standard efficacy parameters were also documented in the study.

Patient exposure

Pivotal study BAY 94-9027 / 21824

In this study, 40 participants were enrolled and screened, of which 35 participants received treatment and 32 participants completed Part A. 35 participants were included in the Safety analysis set.

Adverse events

Pivotal study BAY 94-9027 / 21824

Treatment-emergent AEs (TEAEs) were defined as events starting with the first dose of study drug and up to 7 days after the last dose or last visit in Study Part A. Disease-related events (bleeding events) were not considered AEs but were included in the efficacy assessment. If a bleed fulfilled the definition of an SAE, it was documented as such.

More than half of the participants (60%) experienced at least one TEAE, all of which were mild or moderate in intensity. One participant (2.9%) reported abdominal pain, classified as a moderate-intensity SAE. 3 participants experienced TEAEs considered to be related to study drug: drug ineffective, infusion site pain, and injection site pruritus.

No other TEAEs of special interest were reported. TEAEs related to protocol-required procedures were reported for 3 participants: infusion site pain and injection site pruritus, both of which were also reported as drug-related events; and injection site rash.

Table 14 TEAEs: overall summary of number of participants (SAF)

	Total N=35 (100%)
Number (%) of participants with adverse events	
Any AE	21 (60.0%)
Maximum intensity for any AE	
MILD	14 (40.0%)
MODERATE	7 (20.0%)
Any study drug-related AE	3 (8.6%)
Maximum intensity for study drug-related AE	
MODERATE	3 (8.6%)
Any AE related to procedures required by the protocol	3 (8.6%)
Any AE leading to discontinuation of study drug	0
Any AE of special interest	1 (2.9%)
Any SAE	1 (2.9%)
Any study drug-related SAE	0
Any SAE related to procedures required by the protocol	0
Any SAE leading to discontinuation of study drug	0
AE with outcome death	0
Number (%) of participants with adverse events	

The most frequently reported TEAES mapped to the MedDRA SOCs infections and infestations, general disorders and administration site conditions, and gastrointestinal disorders affecting 11 (31.4%), 8 (22.9%), and 7 (20.0%) participants, respectively. The most frequently reported PTs were cough (4 participants), headache, influenza and pyrexia (3 participants each).

Three participants reported TEAEs that were assessed by the reporting investigators as related to procedures required by the protocol. For 2 of these participants, the TEAEs presenting symptoms of injection site reactions (infusion site pain and injection site pruritus) were also assessed as related to the study drug. A TEAE of similar classification was reported for the third participant: injection site rash. However, this TEAE was considered by the investigator as not related to the study drug but to the intravenous infusion. It lasted for 15 days, was of mild intensity and was resolved without any treatment. All TEAEs were of mild or moderate intensity and had the outcome recovered/resolved.

Table 15 Number of participants with common (≥5% in the analysis set) TEAEs by Primary SOC and PT (SAF).

Primary system organ class Preferred term MedDRA version 26.1	Total N=35 (100%)
Number (%) of participants with at least one such adverse event	21 (60.0%)
Eye disorders	2 (5.7%)
Gastrointestinal disorders	7 (20.0%)
Abdominal pain	2 (5.7%)
General disorders and administration site conditions	8 (22.9%)
Pyrexia	3 (8.6%)
Immune system disorders	2 (5.7%)
Infections and infestations	11 (31.4%)
Influenza	3 (8.6%)
Nasopharyngitis	2 (5.7%)
Sinusitis	2 (5.7%)
Viral pharyngitis	2 (5.7%)
Injury, poisoning and procedural complications	4 (11.4%)
Musculoskeletal and connective tissue disorders	4 (11.4%)
Pain in extremity	2 (5.7%)
Nervous system disorders	4 (11.4%)
Headache	3 (8.6%)
Respiratory, thoracic and mediastinal disorders	6 (17.1%)
Cough	4 (11.4%)

Study drug-related AEs

Three participants (8.6%) experienced TEAEs that were considered to be study drug-related by the investigator. All study drug-related TEAEs were of mild or moderate intensity and all but 1 were recovered/resolved at the end of Study Part A.

The drug related TEAEare described below. No new study drug-related TEAEs occurred compared with previous studies.

• One child experienced LoE based on a very low recovery reported as an AE of moderate intensity, which started after 2 EDs. The investigator considered it to be study drug-related, and Jivi treatment was discontinued after 5 EDs. The participant restarted treatment 2 months later after the disappearance of anti-PEG antibodies without any immune reaction and with normal recovery. During the discontinuation of Jivi treatment, the participant received his previous FVIII treatment.

• One child experienced infusion site pain beginning on Day 1. The TEAE varied between mild and moderate intensity and was assessed by the reporting investigator as related to study drug and to protocol-required procedures. This TEAE was ongoing at end of Study Part A.

• One child experienced injection site pruritus on Study Day 1. This AE was classified as moderate, was assessed by the investigator as related to study drug, and as related to protocol-required procedures. It was resolved without any treatment. The participant withdrew from the study before the 4th ED due to withdrawal by parent/guardian.

Table 16 Number of participants with study drug-related TEAEs by SOC and PT (SAF)

Primary system organ class Preferred term MedDRA version 25.0	Total N=35 (100%)
Number (%) of participants with at least one such adverse event	3 (8.6%)
General disorders and administration site conditions	3 (8.6%)
Drug ineffective	1 (2.9%)
Infusion site pain	1 (2.9%)
Injection site pruritus	1 (2.9%)

Adverse events of special interest

Hypersensitivity reaction to study drug was not reported for any participant. LoE was observed for 1 participant, a child, after the 2nd ED due to very low recovery (0.08 kg/dL with post-infusion FVIII activity of 4.5% 30 minutes after the 3rd infusion). This occurred in the presence of high-titer IgM anti-PEG antibodies (1:16 increasing to 1:64 on 4th ED), resulting in a laboratory-based diagnosis of LoE of the study drug. Subsequently, the antibody titer decreased, and the recovery increased to 0.45 on the 5th ED. The participant discontinued study drug and returned to his prior FVIII medication until the antibodies disappeared. After the disappearance of anti-PEG antibodies, the participant restarted Jivi treatment 2 months later, without presenting any immune reaction, exhibiting normal recovery, and continuing treatment in the Study Part B. It is important to note that the participant experienced bacterial pneumonia with fever and tachycardia after the 2nd ED. The activation of the immune system by the bacterial infection may have triggered the unspecific immune response to PEG.

Serious adverse event/deaths/other significant events

One SAE of moderate intensity (abdominal pain) was reported for 1 (2.9%) participant. This SAE started 26 days after the study treatment initiation, lasted 2 days and led to a hospitalization. It was resolved by the end of Study Part A. The investigator assessed the event as unrelated to study drug and provided an alternative explanation as possible gastroenteritis. No study drug-related SAE was reported.

There were no TEAEs with the outcome death.

Laboratory findings

Pivotal study BAY 94-9027 / 21824

None of the treatment-emergent shifts were considered clinically relevant in this population and none were reported as an AE by the investigator.

Table 17 Treatment-emergent laboratory abnormalities by laboratory category and treatment: number of participants (SAF)

Laboratory variable	TOTAL (N=35) Num/Den(%)
High laboratory abnormalities	
GENERAL CHEMISTRY	
Blood Urea Nitrogen (mg/dL) in Serum of Plasma - Calculated (Factor 2.8)	3/15 (20.0%)
Sodium (mmol/L) in Serum or Plasma	3/10 (30.0%)
HEMATOLOGY	
Basophils/Leukocytes (%) in Blood – Calculated	2/29 (6.9%)
Eosinophils/Leukocytes (%) in Blood – Calculated	2/23 (8.7%)
Hematocrit (%) in Blood – Calculated	5/14 (35.7%)
Lymphocytes/Leukocytes (%) in Blood – Calculated	1/28 (3.6%)
Monocytes/Leukocytes (%) in Blood – Calculated	3/21 (14.3%)
Monocytes (GIGA/L) in Blood	1/23 (4.3%)
Erythrocytes (T/L) in Blood	2/21 (9.5%)
Urinalysis	
Protein (mg/dL) in Urine	1/14 (7.1%)
Low laboratory abnormalities	
GENERAL CHEMISTRY	
Bicarbonate (mmol/L) in Serum	1/ 1 (100.0%)
Chloride (mmol/L) in Serum or Plasma	1/16 (6.3%)
Creatinine (mg/dL) in Serum or Plasma	1/30 (3.3%)
Cystatin C (ug/L) in Serum	1/17 (5.9%)
HEMATOLOGY	
Neutrophils (GIGA/L) in Blood	3/22 (13.6%)
Platelets (GIGA/L) in Blood	1/23 (4.3%)
Leukocytes (GIGA/L) in Blood	3/22 (13.6%)
Urinalysis	
Kidney Injury Molecule-1 (ug/L) in Urine	7/14 (50.0%)
Lipocalin-2 (ug/L) in Urine	1/20 (5.0%)

High abnormalities: The denominator (Den) represents the number of subjects at baseline with a normal or lower than normal laboratory assessment

Low abnormalities: The denominator (Den) represents the number of subjects at baseline with a normal or higher than normal laboratory assessment

Vital signs

None of the vital sign assessments indicated any clinically relevant change. Mean values for vital signs parameters were comparable before and after infusions at all visits.

Liver enzymes

No hepatic AEs were reported and none of the analyse liver enzymes (bilirubin, AST, and ALT) revealed any clinically relevant change. Mean values for each liver enzyme were comparable before and after 6 months of treatment.

Neurological assessment

At baseline, all participants had normal neurological assessments, and no changes were observed after 6 months of treatment with Jivi.

Biomarkers

Renal biomarkers

No clinically relevant changes were observed in the analysed renal biomarkers (in serum: cystatin C and lipocalin; and in urine: total protein, lipocalin-2, kidney injury molecule 1, albumin, creatinine and the

ratios kidney injury molecule 1/creatinine, albumin/creatinine, and protein/creatinine). Mean values for each renal biomarker were comparable before and after 6 months of treatment.

Immunogenicity

FVIII inhibitors

In the Study Part A, no participants tested positive for FVIII inhibitor.

Antibodies against Jivi or its PEG moiety

For almost all participants, anti-PEG and anti-Jivi antibodies results were negative. Positive antibody results against PEG were detected in 6 participants. Of these, 2 had low-titer anti-PEG IgM antibodies (highest titer 1:2) present before the start of study medication, either at screening or baseline. These antibodies disappeared after the start of study medication.

Out of 32 participants with negative anti-PEG antibody results before the study and at least 4 EDs, 4 developed *de novo* anti-PEG IgM antibodies after the 2nd (2 participants) or 3rd (2 participants) ED. In 3 of these 4 participants, the IgM titers were low (highest titer 1:4) resulting in mildly decreased recovery in 2 participants (the lowest recovery was 0.8 kg/dL. Both of these participants withdrew from the study after 7 EDs, due to parent/guardian decision. One participant with low IgM titers and normal FVIII recovery remained in the study. This participant's anti-PEG IgM was negative at Visit 7 (after 4 weeks).

Among the 4 participants with *de novo* anti-PEG IgM antibodies, 1 exhibited high titers (1:64 at the 3rd ED). This was associated with LoE due to very low FVIII levels post-infusion (FVIII post-infusion; 4.5%, recovery: 0.06 kg/dL), leading to discontinuation of Jivi treatment after 5 EDs (reported as AESI). The participant returned to his previous FVIII treatment. The anti-PEG IgM antibodies decreased to 1:32 after 4 days and were not detected 29 days after study treatment was discontinued. No anti-PEG IgM antibodies were detected after re-introduction of treatment, and the recovery was normal. In 3 out of 4 participants with follow-up data, the anti-PEG IgM antibodies either disappeared (2 participants) or significantly decreased (1 participant, drop-out) during the subsequent visits, indicating their transient nature. In one participant with very low-titer antibodies detected at a single time point, no subsequent values were available due to the family refusing follow-up. No new case of antibody responses against PEG IgM were observed after the 4th ED.

Table 18 Positive ADAs (SAF)

	Any antibody Num/Den(%)	PEG Antibody in Plasma Num/Den(%)	PEG IgM Antibody in Plasma - Num/Den(%)	Jivi Antibody in Plasma Num/Den(%)
Positive ADAs at baseline	3/ 35 (8.6%)	0/ 35	2/ 35 (5.7%)	1/ 35 (2.9%)
Positive ADAs at				
Visit 3	0/ 34	0/ 34	0/ 32	0/ 33
Visit 4	2/ 34 (5.9%)	1/ 34 (2.9%)	2/ 32 (6.3%)	1/ 33 (3.0%)
Visit 5	4/ 34 (11.8%)	1/ 34 (2.9%)	4/ 32 (12.5%)	1/ 33 (3.0%)
Visit 6	0/ 2	0/ 2	0/ 2	0/ 2
Visit 7	0/ 30	0/ 30	0/ 26	0/ 29
Visit 8	0/ 1	0/ 1	0/ 1	0/ 1
Visit 11	0/ 32	0/ 32	0/ 9	0/ 31
Any in-treatment visit	4/ 34 (11.8%)	1/ 34 (2.9%)	4/ 32 (12.5%)	1/ 33 (3.0%)
Last measurement	2/ 34 (5.9%)	0/ 34	2/ 32 (6.3%)	0/ 33

Quantitative PEG measurement

PEG was not detectable in 25 of 35 participants. Positive results in 10 participants were just above the detection limit (between 0.104 and 0.268 mg/L; lower limit of detection: <0.1 mg/L).

Discontinuation due to adverse events

No AE led to permanent discontinuation of study drug. Administration of study drug was discontinued for one participant with an AESI of LoE due to high-titer anti-PEG antibodies and was restarted after disappearance of antibodies.

- **Integrated analysis safety**

The MAH provided integrated analysis which included the following studies:

- Study 21824 (Alfa-PROTECT) study in patients 7-<12 years of age, main study (Part A)
- Study 15912 (PROTECT Kids) in patients <12 years of age, main study excluding patients <7 years of age

Safety analysis set

All safety analyses were performed on the SAF, which includes all patients (all patients aged 7 to <12 years from Alfa-PROTECT and PROTECT Kids main studies) who received at least one infusion of the study drug. Except when mentioned otherwise, all safety analyses present results for the integrated analysis. Likewise, all safety results are presented for the combined Jivi treatment groups and do not distinguish between different regimens.

A total of 60 patients who received at least 1 infusion of study drug were included, none of them prematurely discontinued the study with AE as the main reason.

Table 19 Disposition of patients 7 to <12 years old (all enrolled patients, pooled data)

Number of patients	15912	21824	Total
Enrolled	25 (100.0%)	40 (100.0%)	65 (100.0%)
Did not complete screening	0	4 (10.0%)	4 (6.2%)
Primary reason			
OTHER	0	1 (2.5%)	1 (1.5%)
SCREEN FAILURE	0	3 (7.5%)	3 (4.6%)
Assigned to treatment	25 (100.0%)	36 (100.0%)	61 (100.0%)
Study drug never administered	0	1 (2.8%)	1 (1.6%)
Treated	25 (100.0%)	35 (97.2%)	60 (98.4%)
Treatment phase			
Started	25 (100.0%)	35 (100.0%)	60 (100.0%)
Completed	25 (100.0%)	32 (91.4%)	57 (95.0%)
Did not complete	0	3 (8.6%)	3 (5.0%)
Primary reason			
WITHDRAWAL BY PARENT/GUARDIAN	0	3 (8.6%)	3 (5.0%)

Extent of exposure

The median time in the study was 185 days (range: 7 to 278 days), with a median number of 53 EDs (range: 1 to 63). The majority of patients (n=56, 93.3%) in the pooled population achieved 50 EDs. None of the patients achieved 75 EDs during the main study.

Table 20 Treatment duration and exposure days (SAF, pooled data)

	All prophylaxis (N=60)
Treatment duration (days)	
N	60
Mean (SD)	194.1 (48.2)
Median	185.0
Min, Max	7, 278
Q1, Q3	179.1, 218.1
Time in study (days)	
N	60
Mean (SD)	194.1 (48.2)
Median	185.0
Min, Max	7, 278
Q1, Q3	179.1, 218.1
Exposure days	
N	60
Mean (SD)	51.4 (11.4)
Median	53.0
Min, Max	1, 63
Q1, Q3	52.0, 55.0
Exposure days (category)	
<50 days	4 (6.7%)
≥50-<75 days	56 (93.3%)
≥75-<100 days	0

In terms of total FVIII consumption (prophylaxis and treatment of bleeds) during the period covered in the integrated analysis, the median number of infusions was 53 (range: 1 to 63) for all patients. The median corresponding total dose was $2.6*10^3$IU/kg (range: 0 to 4). The median dose per infusion was 50.5 IU/kg.

- **5-year completers**

Safety analysis set

The safety analysis set (SAF) was identical to the intent-to-treat set (ITT) and included patients from PROTECT Kids and PROTECT VIII who completed at least 5 years of treatment. Safety results are presented by study for the combined Jivi treatment groups and do not distinguish between different regimens.

A total of 75 patients were included in the analyses, and all of them completed extension.

Table 21 Disposition of patients (SAF, 5-year completers)

Number of patients	PROTECT Kids (15912)	PROTECT VIII (13024)
Enrolled in extension	39 (100%)	36 (100%)
Treated in extension	39 (100%)	36 (100%)
Discontinued extension	0	0
Completed extension	39 (100%)	36 (100%)

Extent of exposure

The median total time (including main and extension studies) was approximately 6.1 years in PROTECT Kids study and about 6.2 years in PROTECT VIII study.

Table 22 Treatment duration and exposure days (SAF, 5-year completers)

	PROTECT Kids (15912) N = 39	PROTECT VIII (13024) N = 36
Time in study (days)		
Mean (SD)	2207.0 (129.2)	2210.4 (203.9)
Median	2235.8	2250.4
Min, Max	1896; 2396	1837, 2554
Q1, Q3	2118.0, 2296,8	2025.3, 2362.9
Exposure days		
Mean (SD)	493.9 (102.0)	443.1 (94.0)
Median	477.0	428.5
Min, Max	311; 671	293, 698
Q1, Q3	430.0, 602.0	375.0, 491.5

Demographic and other characteristics of study population

Safety pool

Demographic and baseline characteristics of the safety population included in the integrated analysis are detailed in Table 23.

Table 23 Demographics and other baseline characteristics (SAF, pooled data)

	All prophylaxis N=60 (100%)
Sex	
Male	60 (100.0%)
Race	
White	96.7%
Not Reported	3.3%
Ethnicity	
Not Hispanic or Latino	68.3%
Hispanic or Latino	28.3%
Not Reported	3.3%
Age (years)	
N	60
Mean (SD)	8.77 (1.31)
Median	9.00
Min, Max	7.0, 11.0
Age group	
7 - <9 years	28 (46.7%)
9 - <12 years	32 (53.3%)
Baseline Weight (kg)	
N	60
Mean (SD)	33.74 (8.41)
Median	31.20
Min, Max	23.4, 56.1
Baseline Height (cm)	
N	60
Mean (SD)	137.34 (8.32)
Median	137.00

	All prophylaxis N=60 (100%)
Min, Max	122.0, 155.0
Baseline Body Mass Index (kg/m^2)	
N	60
Mean (SD)	17.62 (3.03)
Median	16.80
Min, Max	13.3, 26.6

Prior FVIII treatment

Because only PTPs were enrolled in both studies, all patients had received prior FVIII treatment for ≥50 EDs. 53 (88.3%) patients in the pooled population had received regular FVIII prophylaxis prior to the studies, while prior FVIII treatment was episodic (on-demand) for 7 (11.7%) patients.

5-year completers

Demographic and disease characteristics of patients from the PROTECT Kids and PROTECT VIII studies who completed ≥5 years of treatment are detailed in **Table 24**.

Table 24 Demographics and other baseline characteristics (SAF, 5-year completers)

	PROTECT Kids (15912) N = 39	PROTECT VIII (13024) N = 36
Sex		
Male	39 (100%)	36 (100%)
Race		
White	92.3%	36 (100%)
Black or African American	2.6%	
Asian	2.6%	
American Indian or Alaska Native	2.6%	
Age at enrollment (years)		
Mean (SD)	6.4 (2.9)	36.3 (13.0)
Median	6.0	35.5
Min, Max	2, 11	12, 59
Age at enrollment (years) by age group		
<6 years		not applicable
n	17	

Mean (SD)	3.5 (1.1)	
Median	3.0	
Min, Max	2, 5	
6-<12 years		
n	22	
Mean (SD)	8.6 (1.6)	
Median	9.0	
Min, Max	6, 11	
Approximate age at end of extension (years)		
Mean (SD)	13.2 (3.0)	42.8 (13.2)
Median	13.0	42.5
Min, Max	8, 18	19, 66
Age group at end of extension		
<12 years	13 (33.3%)	
≥12 - 17 years	26 (66.7%)	
18 – <35 years		10 (27.8%)
≥35 years		26 (72.2%)
Baseline weight (kg)		
Mean (SD)	25.2 (8.3)	80.9 (16.8)
Median	25.0	77.4
Min, Max	14, 44	48, 119
Baseline height (cm)		
Mean (SD)	121.4 (17.7)	177.1 (8.3)
Median	122.0	177.8
Min, Max	90, 150	155, 190
Weight at end of extension (kg)		not available
Mean (SD)	52.3 (17.9)	
Median	55.0	
Min, Max	26, 94	
Height at end of extension (cm)		not available
Mean (SD)	158.7 (17.5)	
Median	162.5	
Min, Max	129, 183	

Body Mass Index at end of extension(kg/m^2)		not available
Mean (SD)	20.2 (4.0)	
Median	18.8	
Min, Max	15, 31	

Analysis of adverse events (pooled data)

TEAEs were defined as those that started after the first dose of study intervention and up to 7 days after the last dose received during the main study part (PROTECT Kids) or Part A (Alfa-PROTECT).

More than half (n=38, 63.3%) of patients experienced at least one TEAE, 6.7% experienced events considered to be related to study drug, and 5.0% experienced events considered to be related to procedures required by the protocol. Most TEAEs were mild or moderate in intensity, while 3.3% of patients had events considered to be severe. None of the patients permanently discontinued the study drug due to TEAEs.

Treatment-emergent SAEs were reported in 3 patients (5.0%). None of the SAEs were considered to be related to study drug or related to procedures required by the protocol, and there were no SAEs that resulted in the discontinuation of study drug.

No patient died during the clinical development program of Jivi.

Table 25 Overall summary of number of patients with TEAEs (SAF)

	All prophylaxis N=60 (100%)
Number (%) of patients with TEAEs	
Any AE	38 (63.3%)
Maximum intensity for any AE	
MILD	25 (41.7%)
MODERATE	11 (18.3%)
SEVERE	2 (3.3%)
Any study drug-related AE	4 (6.7%)
Maximum intensity for study drug-related AE	
MILD	1 (1.7%)
MODERATE	3 (5.0%)
Any AE related to procedures required by the protocol	3 (5.0%)
Any AE leading to discontinuation of study drug	0
Any AE of special interest	1 (1.7%)
Any SAE	3 (5.0%)

Any study drug-related SAE	0
Any SAE related to procedures required by the protocol	0
Any SAE leading to discontinuation of study drug	0
AE with outcome death	0

Common adverse events

Treatment-emergent adverse events

The most commonly reported TEAEs by PT were headache (9 patients, 15.0%), pyrexia and cough (5 patients each, 8.3%), and viral infection, pain in extremity and oropharyngeal pain (4 patients each, 6.7%).

Most TEAEs were mild or moderate in intensity. 2 patients reported an event which was considered to be severe (gastroenteritis in 1 patient; haemorrhage intracranial, subarachnoid haemorrhage and device connection issue in 1 patient).

Table 26 Common (≥5%) TEAEs: number of patients by primary SOC and PT (SAF, pooled data)

Primary SOC **PT** **MedDRA Version 26.1**	**All prophylaxis** **N=60 (100%)**
Number (%) of patients with at least one such AE	38 (63.3%)
Ear and labyrinth disorders	3 (5.0%)
Eye disorders	3 (5.0%)
Gastrointestinal disorders	13 (21.7%)
Abdominal pain upper	3 (5.0%)
Vomiting	3 (5.0%)
General disorders and administration site conditions	13 (21.7%)
Pyrexia	5 (8.3%)
Immune system disorders	3 (5.0%)
Infections and infestations	22 (36.7%)
Gastroenteritis	3 (5.0%)
Influenza	3 (5.0%)
Nasopharyngitis	3 (5.0%)
Sinusitis	3 (5.0%)
Tonsillitis	3 (5.0%)
Viral infection	4 (6.7%)

Primary SOC PT MedDRA Version 26.1	All prophylaxis N=60 (100%)
Injury, poisoning and procedural complications	7 (11.7%)
Musculoskeletal and connective tissue disorders	10 (16.7%)
Arthralgia	3 (5.0%)
Pain in extremity	4 (6.7%)
Nervous system disorders	10 (16.7%)
Headache	9 (15.0%)
Respiratory, thoracic and mediastinal disorders	12 (20.0%)
Cough	5 (8.3%)
Epistaxis	3 (5.0%)
Oropharyngeal pain	4 (6.7%)
Skin and subcutaneous tissue disorders	5 (8.3%)

AEs are sorted by alphabetical order of the MedDRA classification.
A patient is counted only once within each primary SOC and PT.

Study drug-related TEAEs

Study drug-related TEAEs were reported for 4 (6.7%) patients. All drug-related events were reported in 1 patient each.

Table 27 Number of patients with study drug-related TEAEs (SAF, pooled data)

Primary system organ class Preferred term MedDRA version 26.1	All prophylaxis N=60 (100%)
Number (%) of patients with at least one such AE	4 (6.7%)
General disorders and administration site conditions	3 (5.0%)
Drug ineffective	1 (1.7%)
Infusion site pain	1 (1.7%)
Injection site pruritus	1 (1.7%)
Respiratory, thoracic and mediastinal disorders	1 (1.7%)
Epistaxis	1 (1.7%)

AEs are sorted by alphabetical order of the MedDRA classification.
A patient is counted only once within each primary SOC and PT
All drug-related TEAEs were mild or moderate in intensity.

TEAEs related to procedures required by the protocol

TEAEs related to protocol-required procedures were reported for 3 (5.0%) patients (infusion site pain, injection site pruritus (both also reported as drug-related), and injection site rash. All TEAEs related to protocol-required procedures were mild or moderate in intensity.

Deaths

No patient died during the clinical development program of Jivi.

Other serious adverse events

Treatment-emergent SAEs were reported for 3 (5.0%) patients. In total, 8 SAEs (PT: photophobia, abdominal pain, nausea, gastroenteritis, haemorrhage intracranial, headache, subarachnoid haemorrhage and device connection issue) were reported in 1 patient each.

None of the treatment-emergent SAEs was considered drug-related.

Adverse events of special interest

Hypersensitivity reactions and LoE were defined as AESIs in the Alfa-PROTECT and PROTECT Kids studies. Allergic type hypersensitivity reactions are a known and listed ADRs for FVIII products and have been reported with use of Jivi. Hypersensitivity reactions could also be related to antibodies against PEG. LoE of the drug product has also been reported in children <6 years of age and has been associated with the development of IgM antibodies to PEG. All such reported events occurred early in treatment, within the first 4 EDs.

In the event of such a hypersensitivity reaction or clinical suspicion of LoE of the treatment product, antibody and inhibitor testing were to be performed. LoE was documented by pre- and post-FVIII levels around an injection of Jivi, analyzed in the central laboratory.

Due to the expected low incidence of AESIs, a Bayesian model combining the outcome of Alfa-PROTECT with information from the PROTECT Kids study was pre-specified in the Alfa-PROTECT protocol to estimate the probability of AESIs associated with the first 4 EDs in the 7 to <12 years age group. This analysis was done on the modified SAF, defined as all SAF patients who did not discontinue for any reason other than AESI prior to the 4^{th} ED. In the Alfa-PROTECT study, one of 34 patients in the modified SAF experienced an AESI during the first 4 EDs leading to temporarily Jivi treatment discontinuation. No AESIs were reported in children aged 7 to <12 years in the PROTECT Kids study. No patient presented a hypersensitivity reaction against Jivi.

Based on the 59 patients (34 from Alfa-PROTECT with 1 AESI and 25 of 7 to <12 years of age from PROTECT Kids with 0 AESIs) and using a Bayesian beta-binomial model, the mean and median of the posterior distribution of the true incidence of AESI in the age group 7 to <12 years were 2.1% and 1.59%, respectively. The posterior probability that the incidence of AESI was <5% was 92.2%.

The crude incidence of AESIs based on the pooled SAF was 1.7% (1/60 patients).

Table 28 AESIs (SAF, pooled data)

	All prophylaxis N=60 (100%)
Number (%) of patients with treatment-emergent AESIs	1 (1.7%)
Drug ineffective	1 (1.7%)

Note: Treatment-emergent AESIs related to the first 4 EDs are included in this summary.

Adverse events leading to discontinuation

None of the patients permanently discontinued their participation in the study due to a TEAE.

One patient temporarily discontinued Jivi treatment due to the TEAE 'drug ineffective' during the first 4 EDs and was successfully restarted on Jivi treatment 2 months later without any clinical or laboratory immune response to the drug.

Analysis of adverse events by organ system or syndrome

Renal disorders

TEAEs related to renal function were not reported in the pooled population.

Nervous system disorders/neurological examinations

Among patients in the pooled population, 10 (16.7%) patients experienced an event within the SOC *Nervous system disorders*. The most frequent event reported in this SOC was headache (n=9, 15.0%), which was not considered to be related to study drug. Most headaches (n=8, 13.3%) were mild in intensity. All other events were single occurrences that were assessed as mild (15.0%) in intensity, except for haemorrhage intracranial and subarachnoid haemorrhage that were both reported as severe in 1 patient in the PROTECT Kids study. This severe event was considered serious and not related to the study drug. No findings were reported for neurological examinations.

Adverse events (5-year completers)

TEAEs were defined as AEs that started after the first dose of study intervention and up to 7 days after the last dose. Only data from the extension studies are presented.

Most patients in both studies who completed ≥5 years of treatment experienced TEAEs during the extension. Treatment-emergent SAEs were reported for approximately 41% of patients in both studies, of which 2 were assessed as related to the study drug by the investigator (suspected FVIII inhibitor).

Table 29 Overall summary of number of patients with TEAEs (SAF, 5-year completers)

	PROTECT Kids (15912) N = 39	PROTECT VIII (13024) N = 36
Number (%) of patients with TEAEs	37 (94.9%)	35 (97.2%)
Maximum intensity for any TEAEs		
MILD	2 (5.1%)	3 (8.3%)

	PROTECT Kids (15912)	PROTECT VIII (13024)
	N = 39	N = 36
MODERATE	30 (76.9%)	22 (61.1%)
SEVERE	5 (12.8%)	10 (27.8%)
Any study drug-related AE	4 (10.3%)	5 (13.9%)
Maximum intensity for study drug-related TEAE		
MILD	2 (5.1%)	3 (8.3%)
MODERATE	1 (2.6%)	2 (5.6%)
SEVERE	1 (2.6%)	0
Any AE related to procedures required by the protocol	1 (2.6%)	0
Any AE leading to discontinuation of study drug	0	0
Any treatment-emergent SAE	16 (41.0%)	15 (41.7%)
Any study drug-related SAE	2 (5.1%)	0
Any SAE related to procedures required by the protocol	0	0
AE with outcome death	0	0

Common adverse events

Treatment-emergent adverse events

PROTECT Kids extension study

The highest number of TEAEs was seen in the *Infections and infestations* primary SOC (n=36, 92.3%) The most frequent PT was nasopharyngitis (n = 17, 43.6%). The other most commonly reported PTs were pyrexia (19 patients, 48.7%); headache and cough (14 patients each, 35.9%); and oropharyngeal pain (13 patients, 33.3%). The majority of TEAEs were mild or moderate in intensity. 5 patients reported events which were considered to be severe; one of them was assessed as study drug-related (PT: muscle spasms).

PROTECT VIII extension study

The highest number of TEAEs in the was seen in the *Musculoskeletal and connective tissue disorders* primary SOC (n=30, 83.3%). The most frequent PT was arthralgia (17 patients, 47.2%). The other most commonly reported PTs were nasopharyngitis (14 patients, 38.9%); and headache, upper respiratory tract infection and back pain (7 patients each, 19.4%).

The majority of TEAEs were mild or moderate in intensity. 10 patients reported events which were considered to be severe (none were assessed as related to the study drug).

Study drug-related TEAEs

4 patients in the PROTECT Kids extension study had TEAEs assessed as related to the study drug by the investigator. These events included anti factor VIII antibody positive (3 patients), and arthralgia and muscle spasms (1 patient each). The anti-factor VIII antibody positive events were either mild or moderate in intensity, as the inhibitors were not clinically relevant. However, they were reported as treatment-emergent SAEs in 2 cases in accordance with the protocol but were not confirmed.

Study drug-related TEAEs in the PROTECT VIII extension study were reported for 5 patients: bone marrow oedema, alanine aminotransferase increased, beta 2 microglobulin urine increased, arthralgia, meniscal degeneration and osteoarthritis.

Deaths

No patient died during the clinical development program of Jivi.

Other serious adverse events

In the PROTECT Kids extension study, treatment-emergent SAEs occurred in 41.0% of patients. Two of these SAEs (reported term suspected factor VIII inhibitor, not confirmed) were assessed as study drug-related by the investigator. Other SAEs were mainly reported for single patients, except haemarthrosis (3 patients, 7.7%), abdominal pain, and head injury (2 patients each, 5.1%).

In the PROTECT VIII extension study, treatment-emergent SAEs occurred in 41.7% of patients. None of these events were assessed as study drug-related by the investigator. SAEs were mainly reported for single patients, except tooth impacted and haemophilic arthropathy (2 patients each, 5.6%).

Adverse events of special interest

In PROTECT Kids study, hypersensitivity and lack of efficacy were defined as AESIs. The PROTECT VIII study protocol did not provide a specific definition for AESIs; however, AEs such as unexpected bleeds or hypersensitivity reactions were monitored.

No AESIs were reported during either PROTECT Kids or PROTECT VIII extension studies.

Adverse events leading to discontinuation

The analyzed safety set included only patients who were treated for at least 5 years, and there were no discontinuations in this population. For information regarding discontinuations during the extension studies, see the respective study reports.

Analysis of adverse events by organ system or syndrome

Renal disorders

No AEs related to renal disorders were reported in the PROTECT Kids extension study.

In the PROTECT VIII extension study, 5 patients experienced AEs in the *Renal and urinary disorders* SOC. One 43-year-old patient with a history of nephrolithiasis requiring multiple surgical interventions in the past was hospitalized twice during the study due to renal complications: once after almost 2 years and again after almost 4.5 years in the extension. The PTs for this patient included nephrolithiasis, hydronephrosis, ureteral stent insertion, renal stone removal, and renal colic. These events were serious, of severe intensity, and classified as not related to study drug.

Other AEs related to renal and urinary disorders included haematuria, hydronephrosis, hydroureter, lower urinary tract symptoms, nephrolithiasis and renal colic. None of these were classified as related to the study drug. No AEs of impaired renal function or renal failure was reported.

Nervous system disorders/neurological examinations

Events within the SOC *Nervous system disorders* were reported for 41.0% of patients in the PROTECT Kids extension study and 33.3% of patients in the PROTECT VIII extension study. The majority of these events were headaches (35.9% and 19.4%, respectively). Other TEAEs were mainly reported for single patients, and none were assessed as related to the study drug.

No abnormal neurological examination findings were reported in either extension study.

Clinical laboratory evaluations

Safety pool

General safety laboratory evaluations

General safety laboratory evaluations included complete blood count, serum chemistry, and urinalysis. In general, none of the treatment-emergent shifts in safety laboratory evaluations were considered clinically meaningful.

Immunogenicity

To evaluate immunogenicity of Jivi, FVIII inhibitors and antibodies against Jivi or its PEG moiety were investigated. During the Alfa-PROTECT study, patients were to be tested for immunogenicity at screening, baseline, at regular visits throughout the study, at the end of Part A/early termination visit, or in case of suspicion of LoE/hypersensitivity. A similar schedule was followed for PROTECT Kids study.

FVIII inhibitors

FVIII inhibitor testing was done according to the Nijmegen-modified Bethesda assay. A positive inhibitor test was defined with a threshold of ≥0.6 BU/mL at the central laboratory. Only inhibitors confirmed by a second positive measurement were considered positive in the analysis.

No patient developed an inhibitor during the study.

Antibodies against Jivi or its PEG moiety

ADAs are binding antibodies against Jivi or its PEG moiety.

All patients were tested for the development of ADAs (anti- PEG and anti-PEG IgM).

The following ADAs were measured:

Anti-Jivi binding antibody, which is an unspecific antibody to any part of the molecule, such as the FVIII protein or PEG moiety. This was a screening test for any antibody isotype.

Anti-PEG antibody, which is an antibody against the PEG moiety across all isotypes (IgG, IgM, IgE, and IgA) and IgM antibodies only, determined by a confirmatory assay step of the anti-Jivi binding antibody assay using Cys-Linker PEG to compete for binding.

At baseline, 5 patients presented a positive result: 1 patient showing anti-Jivi antibodies, 2 patients showing both anti-Jivi and anti-PEG antibodies, and 2 patients only showing anti-PEG IgM antibodies, all of which were very low titers (1:1 up to 1:4) and disappeared after start of treatment within the first 2 weeks. All results were negative at the last measurement.

Treatment-emergent anti-PEG IgM antibodies were observed in 4 patients. All results were negative at the last measurement, except for 2 patients who discontinued for reasons other than AE after a few exposures, and for whom no follow-up was available.

In all cases, positive de novo antibodies were detected after the second ED at Visit 3 (before third exposure) or 4 (before fourth exposure). Anti-PEG antibodies were of the IgM isotype and titers were very low except for one patient who presented high titer anti-PEG IgM antibodies.

This patient was also transiently positive for anti-Jivi antibodies at the same time. All results were negative at the final visit.

Quantitative PEG measurements

Plasma PEG levels were below the lower limit of <0.1 mg/L for all patients in the PROTECT Kids study. Similarly, in the Alfa-PROTECT study PEG was not detectable for most patients, except for 10 patients who had single positive PEG results just above the detection limit (between 0.104 and 0.268 mg/L).

Renal function and renal biomarkers

Renal function

Analyses of creatinine in serum for patients in the pooled safety population are provided in their respective CSRs. There were no changes in this parameter from baseline to end of main study (PROTECT Kids)/study Part A (Alfa-PROTECT).

Renal biomarkers

The measurement of kidney function is commonly made using serum creatinine, blood urea nitrogen, and urinalysis; no changes were observed up to the end of the main trial. Additional exploratory renal biomarkers were measured during the extension study in PROTECT Kids and during Alfa-PROTECT. Results are available at both baseline and the final in-treatment visit for the Alfa-PROTECT study Part A**.** Baseline values are not available for the PROTECT Kids study.

5-year completers

Safety laboratory evaluations

In the PROTECT Kids and PROTECT VIII extension studies, the laboratory safety parameters included immunogenicity assessment, renal function and renal biomarkers, and PEG quantification in plasma.

Immunogenicity

FVIII inhibitors

During the PROTECT Kids extension study, FVIII inhibitor levels were detected above the limit for positivity (≥ 0.6 BU/mL) in 3 patients. Two events were reported as SAEs suspected Factor VIII inhibitor. One event (PT: anti factor VIII antibody positive) was reported as a non-serious AE. No inhibitors were confirmed, as all patients had negative results in the second test. The ELISA assay for anti-Jivi binding antibodies was negative at the same time points for all 3 patients. For all occurrences, the patients did not present any clinical signs of an inhibitor.

No patients in the PROTECT VIII extension study had confirmed positive FVIII inhibitor results above the limit for positivity. One positive result of 1.4 BU/mL was not confirmed at re-test.

Antibodies against Jivi or its PEG moiety

During the PROTECT Kids extension study, one patient had a positive result for anti-Jivi antibodies (Study Day 433, ED 92), with a titer of 1. The Nab level remained <0.6 BU/mL, indicating that the ADA was an unspecific non-neutralizing antibody. All subsequent results were negative, and this finding was not accompanied by any AE. No patient developed an antibody against PEG.

During the PROTECT VIII extension study, 3 patients had transient positive results for anti-PEG antibodies. In all cases, the antibodies were detected only at a single visit, their titers were very low, and

the results were negative at the final visit. One patient had a positive result for anti-Jivi antibodies at a single visit (Study Day 985, ED 209), in addition to being positive for anti-PEG antibodies at the same visit, both with a titer of 1. Results for Nab were negative, indicating that the antibody did not have any neutralizing activity. Thereafter, until the final visit of the extension, the result was negative for both antibodies. The ADA findings were not accompanied by any AE.

Quantitative PEG measurements

In the PROTECT Kids extension study, there was no evidence of PEG accumulation, and the levels remained below detection limit in most patients. Positive PEG levels were detectable in 11 patients, with the first occurrence after 2-6 years of treatment. In 6 patients, the plasma PEG levels were transiently detectable only at single measurements, with 3 of these occurring at the final extension visit. 5 patients had repeatedly positive results, including at the final extension visit. All positive PEG levels were just above the LLOQ, did not increase over time, or returned below the detection limit. No AEs related to positive PEG plasma levels were reported, and renal biomarkers were within the normal range in these patients. 5 patients experienced SAEs unrelated to PEG levels.

In the PROTECT VIII extension study, 3 patients had detectable PEG levels just above the LLOQ and within the 20% assay variability. In 2 patients, the PEG measurement was transiently positive and not detectable at the final visit. For one patient, PEG was detectable in plasma only at the final visit. Renal biomarkers were in the normal range for all 3 patients.

Renal function and renal biomarkers

The determination of exploratory renal biomarkers was added via an amendment to both protocols (PROTECT Kids and PROTECT VIII) while the studies were ongoing. Several exploratory renal biomarkers were measured in serum (cystatin C, lipocalin 2) and in urine (albumin, total protein, beta-2 microglobulin, KIM-1) during the last 2 years in the extension studies (year 4 – 6 after the start of treatment). In PROTECT VIII general renal biomarkers such as creatinine, calculated creatinine clearance, BUN and protein in urine were included as standard safety parameters determined in all patients during total time in the extension study.

Overall, there was no trend for an increase in biomarkers over time after a treatment period of 4 – 6 years during any of the two extension studies. Single results outside of the normal range were only minimal deviations, had follow-up values in the normal range, and there was no trend for an increase over time. These results were not clinically relevant and were not correlated with any clinical AE. There was no sign of any tubular or renal damage after ≥5 years of treatment with Jivi.

Hepatic function

Hepatic parameters were assessed only in the PROTECT VIII extension study. Among patients with normal or low baseline values, 6 out of 25 patients (24.0%) presented elevated ALT levels in serum, and 3 of 29 patients (10.3%) presented elevated AST levels in serum. No patients had treatment-emergent increase in bilirubin. These abnormalities are expected due to the high prevalence of hepatitis B or C observed in this patient population.

Post marketing experience

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.

The total distributed volume of Jivi from the start of marketing authorization through 31 Mar 2024 was approximately 5,438 patientyears. Jivi received marketing authorization in 53 countries and is marketed in 31 countries.

To the data lock point of the last PBRER/PSUR No. 8.0 (covering the reporting interval from 29 AUG 2021 to 28 AUG 2023), no new information has arisen that would change the overall benefit-risk evaluation for Jivi when used in the approved indication or require any new risk minimization measures

Cumulatively, at last PBRER data lock point (28 Aug 2023), 19 reports of off-label use in patients <12 years of age were received in the post-marketing period from all post-marketing sources in the company safety database. No new safety concerns have been identified.

There is currently no need for additional risk minimisation activities.

EU PASS (Study 20904, HA-SAFE)

The HA-SAFE study (Study 20904) is an ongoing observational study evaluating long-term safety of real-world treatment with Jivi in previously treated patients with hemophilia A. The study is being conducted at the request of the EMA. The study aims to observe 50 patients for at least 4 years each, in line with the sample size requested by the Authority (EMA) for safety analysis. Assuming a dropout rate of approximately 20% (due to lost to follow-up cases or withdrawals), 60 patients were to be enrolled.

The primary objective of this study is to assess the long-term safety of prophylaxis with Jivi in patients with hemophilia A in a real-world setting through the collection and analysis of AESIs, including those potentially indicative of PEG accumulation. The AESIs include:

Hypersensitivity reactions

Loss of drug effect

Renal impairment

Neurocognitive disorders

Inhibitor development

Additionally, safety is assessed through the thorough collection and analysis of AEs, SAEs, and adverse reactions.

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

The study is ongoing, and enrollment is complete.

Overall, no new safety concern has been identified based on the available data.

2.5.1. Discussion on clinical safety

In total 35 subjects were included in the Safety analysis set in the pivotal study Alfa-PROTECT. 60% of the participants experienced at least one TEAE. No severe TEAE were reported. Only one case of SAE was reported (abdominal pain moderate-intensity, unrelated to study drug). There were no TEAEs with the outcome death.

There were 3 TEAEs considered to be related to study drug: drug ineffective, infusion site pain, and injection site pruritus. One TEAE – injection site rash was considered by the investigator as not related to the study drug but to the intravenous infusion. All TEAEs were of mild or moderate intensity. The participant who experienced injection site pruritus was withdrawn from the study before the 4th ED by parent/guardian. TEAE site pain was ongoing at end of Study Part A.

The LoE was reported based on a very low recovery which started after 2 EDs. However, the participant experienced bacterial pneumonia with fever and tachycardia after the 2nd ED, which could activate the immune system and may have triggered the unspecific immune response to PEG. The treatment was

discontinued after 5 EDs and restarted 2 months later after the disappearance of anti-PEG antibodies without any immune reaction and with normal recovery.

Positive antibody results against PEG were detected in 6 participants, including 2 subjects who had low-titer anti-PEG IgM antibodies (highest titer 1:2) present before the start of study medication and disappeared after the start of study medication.

In total 4 subjects out of 32 with negative anti-PEG antibody results before the study and at least 4 EDs, developed *de novo* anti-PEG IgM antibodies after the 2nd (2 participants) or 3rd (2 participants) ED. In 2 of these 4 subjects decreased recovery was reported and these subjects withdrew from the study after 7 EDs, due to parent/guardian decision. One subject who had low IgM titers and normal FVIII recovery remained at the study.

One subject exhibited high titers (1:64 at the 3rd ED), which was associated with LoE due to very low FVIII levels post-infusion (FVIII post-infusion; 4.5%, recovery: 0.06 kg/dL), leading to discontinuation of Jivi treatment after 5 Eds. The treatment was reintroduced 2 months later with no anti-PEG IgM antibodies detected and normal recovery. In one of the subjects who discontinued the anti-PEG IgM antibodies significantly decreased, data from the second participant are not available.

Overall, it can be agreed that based on the results of the pivotal study, safety profile of Jivi reported in subjects 7-<12 years of age can be considered comparable to subjects above 12 years of age and older.

The MAH provided integrated analysis which included safety data from a pivotal study Alfa-PROTECT and PROTECT KIDS from all patients aged 7 to <12 years. A total of 60 patients who received at least 1 infusion of study drug were included in the analysis. 93.3% of patients in the pooled population achieved ≥50 days of exposure. The median dose per infusion was 50.5 IU/kg.

63.3% of patients in the safety pool experienced at least one TEAE, including 6.7% who experienced events considered to be related to study drug. 2 patients (3.3%) experienced events considered to be severe, however, none of the patients permanently discontinued the study drug due to TEAEs.

Treatment-emergent SAEs were reported in 3 patients, but none of the SAEs were considered to be related to study drug and there were no SAEs that resulted in the discontinuation of study drug. No patient died during the clinical development program of Jivi.

15% of subjects (9 in total) experienced TEAE headache, 8.3% TEAEs pyrexia and cough. 2 subjects reported severe TEAEs – gastroenteritis in 1 patient and haemorrhage intracranial, subarachnoid haemorrhage and device connection issue in 1 patient. Infections and infestations were reported in 22 subjects (36.7%) and included cases of gastroenteritis (5%), influenza (5%), nasopharyngitis (5%), sinusitis (5%), tonsilitis (5%) and viral infection (6.7%). The overall incidence of infections and infestations is considered quite high, however, the lack of control group prevents definitive conclusions. There were in total 4 drug-related TEAEs.

Study drug-related TEAEs were reported for 4 (6.7%) patients. All drug-related events were reported in 1 patient each (drug ineffective, infusion site pain, injection site pruritus, epistaxis). All drug-related TEAEs were mild or moderate in intensity. There were no death cases in the JIVI clinical development programme. There were in total 8 serious AE reported in 3 subjects (photophobia, abdominal pain, nausea, gastroenteritis, haemorrhage intracranial, headache, subarachnoid haemorrhage and device connection issue) were reported in 1 patient each.

None of the treatment-emergent SAEs was considered drug-related.

There was one case of LoE (AESI) in the safety data pool. No patient presented a hypersensitivity reaction against Jivi. The MAH used a Bayesian model combining the outcome of Alfa-PROTECT with information from the PROTECT Kids study to estimate the probability of AESIs associated with the first 4 EDs in the 7 to <12 years age group.

Based on the 59 patients (34 from Alfa-PROTECT with 1 AESI and 25 of 7 to <12 years of age from PROTECT Kids with 0 AESIs) and using a Bayesian beta-binomial model, the mean and median of the posterior distribution of the true incidence of AESI in the age group 7 to <12 years were 2.1% and 1.59%, respectively. The posterior probability that the incidence of AESI was <5% was 92.2%. The crude incidence of AESIs based on the pooled SAF was 1.7% (1/60 patients).

None of the patients permanently discontinued their participation in the study due to a TEAE.

One patient temporarily discontinued Jivi treatment due to the TEAE 'drug ineffective' during the first 4 EDs and was successfully restarted on Jivi treatment 2 months later without any clinical or laboratory immune response to the drug.

No patient developed an inhibitor against FVIII during the study.

All patients included in both studies were tested for the development of ADAs (anti- PEG and anti-PEG IgM).

At baseline, 5 patients presented a positive result for anti-Jivi antibodies (1 patient), anti-Jivi and anti-PEG antibodies (2 patients), anti-PEG IgM antibodies (2 patients). However, in all cases very low titers (1:1 up to 1:4) were observed and moreover, it disappeared within 2 weeks after start of treatment. At the last measurement all results were negative.

Treatment-emergent anti-PEG IgM antibodies were observed in 4 patients. In 2 patients at the last measurement the results were negative. However, it was not the case for 2 other patients who discontinued the study. Anti-PEG antibodies were of the IgM isotype and titers were very low except for one patient who presented high titer anti-PEG IgM antibodies and also was transiently positive for anti-Jivi antibodies at the same time.

PEG levels were detectable for 10 patients in Alfa-PROTECT study. Six of these 10 patients reported at least one AE during the study, occurring between 1 and 187 days after the start of treatment. None of these patients reported any AE or clinical sign that could be related to PEG. Most AEs were infectious diseases, and two AEs were considered drug related (ADR: infusion site pain, drug ineffective). All AEs were non-serious. No patient presented any signs of renal or hepatic disease, nor abnormal lab values of hepatic or renal function. It can be concluded that there is no relation between AEs and positive PEG levels and that the positive and very low PEG levels did not have any impact on patients' safety.

Section 4.4 of the SmPC provides the following recommendation: "A clinical immune response associated with anti-PEG antibodies, manifested as symptoms of acute hypersensitivity and/or loss of drug effect has been observed primarily within the first 4 exposure days. Low post-injection factor VIII levels in the absence of detectable factor VIII inhibitors indicate that loss of drug effect is likely due to anti-PEG antibodies; in such cases Jivi should be discontinued and patients switched to a previously effective factor VIII product.
In case of clinical suspicion of loss of therapeutic effect, testing for Factor VIII inhibitors and Factor VIII recovery is recommended.' In addition, 'loss of efficacy associated with PEG antibodies' is an important identified risk in the RMP.

The MAH provided analysis of safety analysis set and included 75 patients from PROTECT Kids and PROTECT VIII who completed at least 5 years of treatment. However, safety data were not distinguished between different regimens.

94.9% and 97.2% of patients included in PROTECT Kids and PROTECT VIII studies who completed ≥5 years of treatment experienced TEAEs during the extension. Severe TEAEs were reported in 12.8% and 27.8% of subjects in PROTECT Kids and PROTECT VIII studies, respectively. Treatment-emergent SAEs were reported for approximately 41% of patients in both studies, of which 2 were assessed as related to the study drug by the investigator. In the PROTECT KIDS extension study, the most frequently reported TEAEs was nasopharyngitis (17 subjects, 43.6%), pyrexia (19 patients, 48.7%), headache and cough (14 patients each, 35.9%) and oropharyngeal pain (13 patients, 33.3%). 5 patients reported severe AE but

only one of them was considered study drug-related (muscle spasms). In PROTECT VIII extension study, the most frequent AE were arthralgia (17 patients, 47.2%), nasopharyngitis (14 patients, 38.9%) and headache, upper respiratory tract infection and back pain (7 patients each, 19.4%). There were in total 10 severe events, but none of them was considered related to the study drug. In total 9 patients reported TEAEs related to the study drug (4 patients in PROTECT KIDS extension study - anti factor VIII antibody positive (3 patients), arthralgia and muscle spasms (1 patient each) and 5 in PROTECT VIII extension study - bone marrow oedema, alanine aminotransferase increased, beta 2 microglobulin urine increased, arthralgia, meniscal degeneration and osteoarthritis). No patient died during the clinical development program of Jivi.

No AESIs were reported during either PROTECT Kids or PROTECT VIII extension studies.

There were 2 discontinuations in the PROTECT Kids extension study, both involving patients <6 years of age. There were 7 discontinuations during the PROTECT VIII extension study. Three were withdrawals by patient, one was lost to follow-up, one by sponsor decision due to a trip abroad, and two of them due to AE - increased liver function tests (AST, ALT, and LDH) of moderate intensity and severe back pain and thrombocytopenia of mild intensity. Since patients who discontinued due to increased liver function had also HIV and chronic Hepatitis C, the discontinuation can be considered not directly related to the study drug.

FVIII inhibitor levels were detected above the limit for positivity in 3 patients in the PROTECT KIDS extension study. No patients in the PROTECT VIII and PROTECT Kids extension studies had confirmed positive FVIII inhibitor results above the limit for positivity.

There were two reported SAEs of intracranial bleeding events in the pooled safety analysis. It was clarified during the procedure that the bleeding events were associated with the surgical procedures and occurred following the interruption of the study drug; therefore, they were all classified as non-drug related.

One patient in the PROTECT Kids extension study had a positive result for anti-Jivi antibodies. 3 patients had transient positive results for anti-PEG antibodies in the PROTECT VIII extension study and one patient had a positive result for anti-Jivi antibodies at a single visit. No AE related to the ADA were reported.

Positive PEG levels were reported in 11 patients in the PROTECT KIDS extension study, including 6 patients in whom plasma PEG levels were detectable transiently at single measurements. All positive PEG levels were just above the LLOQ, did not increase over time. No AEs related to positive PEG plasma levels were reported. 3 patients had detectable PEG levels just above the LLOQ in the PROTECT VIII extension study, including 2 patients with the PEG measurement transiently positive and not detectable at the final visit. No clinically relevant renal abnormalities were reported in these patients. Although the overall number of subjects with detectable plasma PEG levels is not considered negligible, it is acknowledged that no AEs related to positive PEG plasma levels were observed.

2.5.2. Conclusions on clinical safety

Overall, no new safety signals were reported in the proposed population. The safety profile of Jivi can be considered consistent across age groups and support the extension of indication to younger patients.

The following additional recommendation has been added in section 4.4 of the SmPC: In case of clinical suspicion of loss of therapeutic effect, testing for Factor VIII inhibitors and Factor VIII recovery is recommended.' In addition, 'loss of efficacy associated with PEG antibodies' is an important identified risk in the RMP.

In addition, the following warning with regards to decreased factor VIII incremental recovery was added: 'A minor reduction of recovery (recovery around 1 IU/dL per IU/kg) after start of treatment was observed and may be due to transient low titer anti PEG IgM antibodies mainly in children. Low incremental recovery could potentially be associated with reduced efficacy during this time period. Monitoring of

paediatric patients, including monitoring of post dose factor VIII activity, is recommended. If a bleeding is not controlled with the recommended dose and/or the expected Factor VIII activity levels are not attained in the absence of FVIII inhibitors, consider adjusting the dose, dosing frequency or discontinuing the product.'

2.5.3. PSUR cycle

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

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 3.3 is acceptable.

The CHMP endorsed the Risk Management Plan version 3.3 with the following content:

Safety concerns

Table 30 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

Pharmacovigilance plan

Table 31 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 other tissues/organs, hypersensitivity reactions, loss of efficacy, development of FVIII inhibitors	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
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 study results	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 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

Risk minimisation measures

No additional risk minimisation measures are planned.

2.7. Update of the Product information

As a consequence of this new indication, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC were updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s) [e.g. Excipients guideline, storage conditions, Braille, etc…], which were reviewed by QRD and accepted by the CHMP.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet was submitted by the MAH and found acceptable for the following reasons:

Within this application for the grouped Type II Variations the MAH also submits a revised EU-PI. Due to the introduction of new clinical data not all changes that are proposed in the SmPC need to be reflected in the package leaflet.

The indication wording has been modified. Apart from that, the only necessary update in the package leaflet was one more added sentence in PIL section 2 "Warnings", and one more added sentence in PIL section 3 "Prevention of bleeding" – and the deletion of the Northern Ireland local representative local representative address as required by QRD Template version 10.4.

The MAH refers to the successfully user tested package leaflet and the corresponding report that has been received and checked by EMA within the initial MAA (Procedure No. EMEA/H/C/004054/0000), since

- the content of the proposed package leaflet is almost identical
- the key safety information is the same
- the size, format and layout of the printed package leaflet will be the same.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Jivi is indicated for treatment and prophylaxis of bleeding in previously treated patients ≥ 12 years of age with haemophilia A (congenital factor VIII deficiency). Restriction of the indication to patients aged 12 and older was due to safety concerns regarding potential effects of long-term PEG exposure. To support the proposed paediatric extension of the indication, the MAH provided the integrated analysis of Alfa-PROTECT Part A and the PROTECT Kids main study which included data from patients aged 7 to <12 years, focusing on the incidence of immune response to PEG within the first 4 exposure days and its impact on treatment efficacy.

3.1.1. Disease or condition

Haemophilia A (congenital factor VIII [FVIII] deficiency) is a potentially life-threatening or seriously debilitating chronic disease. It is an inherited disease caused by mutations in the gene coding for FVIII which result in FVIII deficiency state.

3.1.2. Available therapies and unmet medical need

Per the current recommendations of the WFH Guidelines for the Management of Haemophilia as well as of many national and international haemophilia organisations, the standard of care for all patients with severe haemophilia A is primary prophylaxis, defined as regular therapy with FVIII replacement products or other haemostasis products to prevent spontaneous bleeding. Primary prophylaxis should be initiated early in life prior to the onset of joint disease, before the second clinically evident joint bleed and before 3 years of age to prevent musculoskeletal complications from recurrent joint and muscle bleeds (Srivastava et al. 2020).

Hemlibra (emicizumab) is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors.

Efanesoctocog alfa (Altuvoct) is a modified recombinant factor VIII that is designed to enhance the hemostatic function. It works by binding to activated factor X (Xa) to facilitate the conversion of prothrombin to thrombin, thereby promoting the clotting cascade effectively. Its unique structure allows for stable interaction with the coagulation system, improving its efficacy in controlling bleeding.

Both Hemlibra and Altuvoct can be used in all age groups.

Another treatment option is gene therapy of haemophilia A, Valoctocogene roxaparvovec (Roctavian), an adeno-associated viral serotype 5 (AAV5) vector containing a B-domain-deleted variant of human FVIII, has the potential to provide sustained FVIII activity levels. Roctavian is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

Episodic or on-demand FVIII treatment, i.e., treating bleeds when they occur, is no longer considered the standard of care for the management of haemophilia as it does not alter the natural history of frequent and recurrent bleeding and related complications. Patients suffering from severe haemophilia A usually receive prophylactic treatment with FVIII products, which requires regular infusion every 2 to 3 days.

3.1.3. Main clinical studies

To support the proposed extension of the indication to PTP patients ≥7 years of age, the MAH submitted results of the pivotal study Alfa-PROTECT, an integrated analysis including results of studies Alfa-PROTECT and PROTECT KIDS (7-<12 years of age) and long-term efficacy data collected in patients who completed at least 5 years of treatment in the PROTECT KIDS study.

The Alfa-PROTECT study is an ongoing open-label, single-group, uncontrolled, prospective, multi-center Phase 3 study to evaluate the safety of Jivi for prophylaxis and treatment of bleeding in previously treated children aged 7 to <12 years with severe haemophilia A who had received prophylaxis treatment before the study (≥50 EDs). The Study consist of two parts (PART A – completed and PART B – ongoing). The main study (Part A) assessed the safety and efficacy of Jivi (at the dose of 40IU/kg up to 60IU/kg at the investigator's discretion) for prophylaxis and treatment of breakthrough bleeding for 6 months and at least 50 EDs. After completion of the main study, patients were offered to continue in the extension study (Part B) for additional 18 months, which will further evaluate the long-term safety, clinical efficacy, and impact of Jivi on health-related QoL. In Part B, each patient will continue their prophylaxis dose regimen from Part A or can be adjusted to 60 IU/kg every 5 days at the investigator's discretion.

3.2. Favourable effects

In the pivotal study Alfa-PROTECT in total 50% participants did not present any bleeds during the study and 71.9% of participants did not experience any joint bleeds. The majority of the reported bleeds (a total of 64 bleeds) were spontaneous (46/64) with 46.9 % skin/mucosa bleeds.

Response to treatment of bleeds was rated as either good or excellent for most bleeds (71.4%). The median ABR (Q1, Q3) for all treated bleeds was 0 (0, 1.9) and the mean (95% CI) ABR based on a negative binomial regression model is 1.33 (95% CI: 0.61, 2.90). The median ABR (Q1, Q3) for each type of treated bleed was 0 (0, 0). When including untreated bleeds, the median ABR (Q1, Q3) was 0.9 (0, 4.9).

The median FVIII recovery across visits in the absence of any anti-PEG antibodies was 1.69 (1.1, 2.9) kg/dL.

In Global Impression of Severity, 40.6% of caregivers and 34.4% of patients reported an improvement.

3.3. Uncertainties and limitations about favourable effects

21 of reported 64 bleeds required treatment. However, it is noted that 11/21 of bleeds that required treatment were trauma-related. Severe intensity was reported for 7.8% of all bleeds and 23.8% of treated bleeds. 47.6% of the treated bleeds were of moderate severity.

LoE was observed for 1 participant, a child, after the 2nd ED due to very low recovery (0.08 kg/dL with post-infusion FVIII activity of 4.5% 30 minutes after the 3rd infusion). This occurred in the presence of high-titer IgM anti-PEG antibodies (1:16 increasing to 1:64 on 4th ED), resulting in a laboratory-based diagnosis of LoE and discontinuation of Jivi treatment after 5 EDs. The following additional recommendation has therefore been added in section 4.4 of the SmPC: In case of clinical suspicion of loss of therapeutic effect, testing for Factor VIII inhibitors and Factor VIII recovery is recommended' together with the following warning with regards to decreased factor VIII incremental recovery: 'A minor reduction of recovery (recovery around 1 IU/dL per IU/kg) after start of treatment was observed and may be due to transient low titer anti PEG IgM antibodies mainly in children. Low incremental recovery could potentially be associated with reduced efficacy during this time period. Monitoring of paediatric patients, including monitoring of post dose factor VIII activity, is recommended. If a bleeding is not controlled with the

recommended dose and/or the expected Factor VIII activity levels are not attained in the absence of FVIII inhibitors, consider adjusting the dose, dosing frequency or discontinuing the product.' In addition, 'loss of efficacy associated with PEG antibodies' is an important identified risk in the RMP.

Poor response to the treatment was reported in one subject. The following statement has been in section 4.8 of the SmPC: 'One child > 7 years, developed high titre neutralising anti-PEG IgM antibodies within the first 4 exposure days associated with loss of drug effect. Antibodies disappeared after discontinuation and patient safely re-started treatment with Jivi 2 months later.

Transient low titre anti-PEG antibodies of the IgM isotype were observed in some patients within the first 4 ED resulting in minor reduction of Jivi recovery.'

In the PRO of Global Impression of Severity only 21.9% of caregivers and 9.4% of patients reported decline of severity.

3.4. Unfavourable effects

60% of the pivotal study participants experienced at least one TEAE.

There were 3 TEAEs considered to be related to study drug: drug ineffective, infusion site pain, and injection site pruritus. All TEAEs were of mild or moderate intensity.

Positive antibody results against PEG were detected in 6 participants.

In total 4 subjects out of 32 developed de novo anti-PEG IgM antibodies after the 2nd (2 participants) or 3rd (2 participants) ED. In 2 of these 4 subjects decreased recovery was reported and these subjects withdrew from the study after 7 EDs, due to parent/guardian decision. One subject who had low IgM titers and normal FVIII recovery remained at the study.

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 32 Effects Table for Jivi paediatric extension of indication

Effect	Short description	Unit	Treatment (n=32)	Uncertainties / Strength of evidence	References
Annualized number of total bleeds	Median (Q1, Q3) All bleeds		0.92 (0, 4.9)	SoE: median ABR for all treated bleeds = 0 (0, 1.9)	Alfa-PROTECT
Response to treatment	EXCELLENT OR GOOD		71.4%		Alfa-PROTECT
Loss of efficacy De novo high titer anti-PEG IgM antibodies			1 patient		Alfa-PROTECT
Positive antibody results against PEG			6 patients		Alfa-PROTECT
de novo low titer anti-PEG IgM antibodies			3 patients		Alfa-PROTECT

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The results of the pivotal study and integrated efficacy analysis can be considered sufficient to demonstrate efficacy of Jivi in the proposed target population of patients. In the pivotal study, the median ABR (Q1, Q3) for all treated bleeds was 0 (0, 1.9) and the mean (95% CI) ABR based on a negative binomial regression model is 1.33 (95% CI: 0.61, 2.90). The median ABR (Q1, Q3) for each type of treated bleed was 0 (0, 0). When including untreated bleeds, the median ABR (Q1, Q3) was 0.9 (0, 4.9). Response to treatment of bleeds was rated as either good or excellent for most bleeds (71.4%). Poor response was reported in one subject.

Overall, based on the results of the pivotal study, the safety profile of Jivi reported in subjects between 7 and 12 years of age can be considered comparable to subjects above 12 years of age and older.

3.7.2. Balance of benefits and risks

Benefit/risk of Jivi is considered positive for the treatment and prophylaxis of bleeding in previously treated patients ≥ 7 years of age with haemophilia A (congenital factor VIII deficiency).

3.7.3. Additional considerations on the benefit-risk balance

Not Applicable.

3.8. Conclusions

The overall B/R of Jivi is positive for the treatment and prophylaxis of bleeding in previously treated patients ⩾ 7 years of age with haemophilia A (congenital factor VIII deficiency).

4. Recommendations

Outcome

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

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

Extension of indication to include treatment and prophylaxis of bleeding in previously treated patients ≥7 years of age with haemophilia A for Jivi, based on integrated analysis results from Part A of the Alfa-PROTECT study (21824) and PROTECT Kids main study (15912). Alfa-PROTECT is a Phase 3, single-group treatment, open-label study to evaluate the safety of BAY 94-9027 infusions for prophylaxis and treatment of bleeding in previously treated children aged 7 to <12 years with severe haemophilia A. PROTECT Kids is a multi-center, Phase 3, non-controlled, open-label trial to evaluate the pharmacokinetics, safety, and efficacy of BAY 94-9027 for prophylaxis and treatment of bleeding in

previously treated children (age <12 years) with severe haemophilia A. As a consequence, sections 2, 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.3 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II, IIIA and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk management plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

At the request of the European Medicines Agency;

Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post Authorisation Safety Study (PASS): In order to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs, the MAH should conduct and submit the results of a non-interventional post-authorisation safety study according to an agreed protocol.	Final study report should be submitted by 31 December 2028

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Jivi is not similar to Altuvoct and Roctavian within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication to include treatment and prophylaxis of bleeding in previously treated patients ⩾7 years of age with haemophilia A for Jivi. In addition, a warning on decreased factor VIII incremental recovery has been added in section 4.4 of the SmPC. Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Jivi-H-C-004054-II-34'