16 October 2025
EMADOC-1700519818-2569488
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Afstyla

Lonoctocog alfa

Procedure no: EMA/PAM/0000282137

Note

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

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Status of this report and steps taken for the assessment			
Current step[1]	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	25 August 2025	25 August 2025
☐	CHMP comments	8 September 2025	8 September 2025
☐	Updated CHMP Rapporteur AR	11 September 2025	N/A
☐	CHMP Request for Supplementary Information	18 September 2025	18 September 2025
	Submission deadline	23 September 2025	25 September 2025
☐	CHMP Rapporteur AR	1 October 2025	30 September 2025
☐	CHMP comments	6 October 2025	6 October 2025
☐	Updated CHMP Rapporteur AR	9 October 2025	N/A
☒	CHMP outcome	16 October 2025	16 October 2025

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1. Introduction

On 27 June 2025, the MAH submitted a completed paediatric study for Afstyla, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study "A Prospective, Non-Interventional Study to Investigate the Effectiveness of Afstyla in Patients with Hemophilia A" (NIS_PVA78092_CSL627) is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

Afstyla is currently authorized in the EU for treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Afstyla can be used for all age groups.

The pharmaceutical formulation is powder and solvent for solution for injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- Study NIS_PVA78092_CSL627, "A Prospective, Non-Interventional Study to Investigate the Effectiveness of Afstyla® in Patients with Hemophilia A"

This non-interventional study NIS_PVA78092_CSL627 was conducted to investigate the use of Afstyla under real-life conditions to confirm the effectiveness and safety of Afstyla established in the pivotal clinical studies in a broader hemophilia A population.

The MAH did not propose an amendment of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet for Afstyla.

2.3.2. Clinical study

Clinical study number and title

Study NIS_PVA78092_CSL627: A Prospective, Non-Interventional Study to Investigate the Effectiveness of Afstyla in Patients with Hemophilia A

Description

This multicenter international NIS included patients with haemophilia A treated with Afstyla. Observational data were collected from participants who were treated with Afstyla, in accordance with clinical practice and the current summary of product characteristics (SmPC), either as long-term prophylaxis (long-term replacement therapy to avoid bleeding), for the prevention of bleeding episodes (short-term replacement therapy to prevent bleeding in a high-risk period, eg, surgery), or on demand (episodic replacement therapy at the time of clinically evident bleeding). No additional diagnostic or monitoring procedures were conducted.

The planned start of data collection was in January 2019. The first participant was enrolled on 26 August 2019. With the planned recruitment period of one year (until Q1 2020) and an observation period of 36 months per participant, the planned end of data collection would have been in Q1 2023. Recruitment was extended until December 2021 and the last participants' visit to study center was on 21 November 2024. Visits to study centers were performed according to clinical practice. Visits to study centers were anticipated to take place approximately every 6 months.

Methods

Study participants

This NIS was conducted in Austria, Belgium, Czech Republic, Germany, Greece, and Hungary with a total of 22 participating study centers and 72 participants. The number of participating haemophilia treatment centers and participants in the single countries were:

- Austria: 2 centers with a total of 9 participants
- Belgium: 1 center with a total of 4 participants
- Czech Republic: 2 centers with a total of 2 participants
- Germany: 12 centers with a total of 43 participants
- Greece: 3 centers with a total of 12 participants
- Hungary: 2 centers with a total of 2 participants.

Inclusion criteria:

- Signed informed consent form (ICF; signature of legal representative for paediatric / adolescents)
- Diagnosed with Haemophilia A
- Receiving Afstyla for treatment and prophylaxis of bleeding episodes.

Exclusion criteria:

- Participation in a clinical trial at the time of enrolment
- Hypersensitivity to the active substance or to any of the excipients
- Known allergic reaction to hamster proteins

- Presence of inhibitors to FVIII or to Afstyla and / or ITI at the time of enrolment.

Treatments

Receiving Afstyla under real-word condition. The number and percentage of participants on each regimen (on demand, prophylaxis, ITI, prevention, missing), (i) irrespective of duration and (ii) for $\geq$ 12 weeks was presented.

Objective(s)

The primary objective of this study was to evaluate the effectiveness of Afstyla in preventing and treating bleeding episodes in routine patient care.

The secondary objectives concerned the evaluation of the:

- Consumption of Afstyla in routine patient care
- Information on the Afstyla treatment regimen used by the patients
- Characteristics of bleeding episodes (eg, severity, location)
- Tolerability and safety of Afstyla.

Other objectives were to evaluate:

- Information on participants' physical activity level
- Participants' joint health status
- Participants' Quality of Life (QoL).

Outcomes/endpoints

The evaluation criteria to address the primary objective of this study were:

- The annualized bleeding rate (ABR) during on-demand treatment and prophylaxis
- The annualized spontaneous bleeding rates (AsBR) during on-demand treatment and prophylaxis
- The haemostatic effectiveness of Afstyla for the treatment of bleeding episodes (number of injections and dose required), including proportion of bleeding episodes requiring 1 or 2 infusions of Afstyla
- Investigator's rating of haemostatic effectiveness of Afstyla for prophylaxis, prevention of non-surgical bleeding episodes and on-demand treatment.

The evaluation criteria to address the secondary objectives of this study were:

- Participants' consumption of Afstyla (overall consumption and consumption for prophylactic treatment)
- Characteristics of bleeding episodes (eg, severity and location)
- The number of participants receiving prophylaxis, including dosing (in international unit [IU]/kg body weight) and infusion frequency during prophylactic treatment
- Safety endpoints:
    - Number of participants developing inhibitors to FVIII or to Afstyla
    - Number, type and severity of adverse events (AEs).

The evaluation criteria to address the other important objectives were:

- Participants' physical activity level assessed by means of a verbal rating scale (VRS)
- Participants' QoL assessed by means of the Haem-A-QoL (for adults) or the Haemo-QoL (for children [age groups 4 to 7 years and 8 to 12 years] and adolescents [aged 13-16 /18 years])
- Participants' joint status assessed by means of the Haemophilia Joint Health Score (HJHS) V2.1.

Sample size

Haemophilia A is a very rare disease hence a limited pool of patients was available for study participation. The sample size was not calculated according to statistical criteria, but was based on practical considerations, ie, the estimated number of suitable participants. The estimated sample size across the participating countries was approximately 120 participants.

Assessor`s comment

The initially planned number of 120 patients was not reached. Since limited availability of patients was already regarded in the sample size calculation, the applicant should explain the reduced number of patients investigated.

Randomisation and blinding (masking)

N/A

Statistical Methods

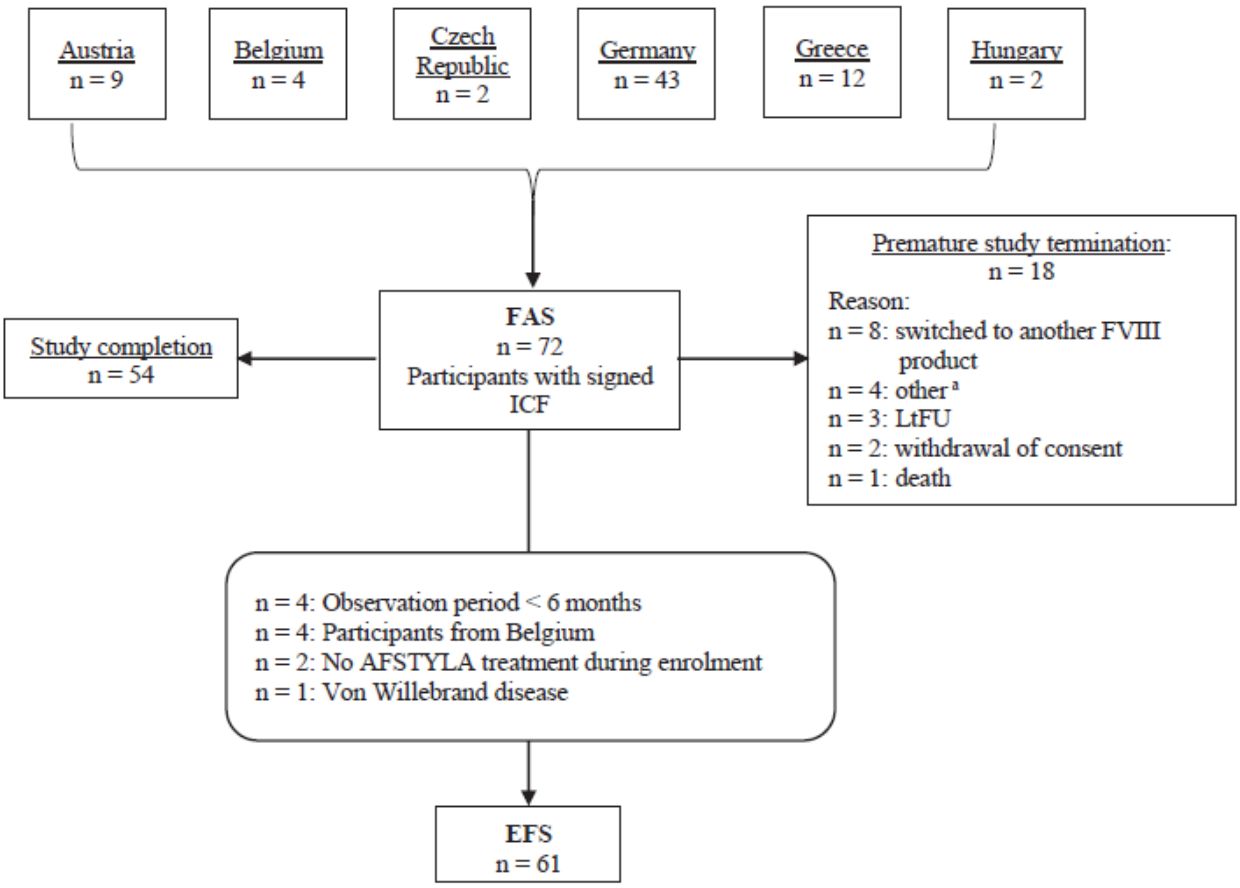
All analyses of this study were exploratory (non-confirmatory) and no formal hypotheses were tested.

Continuous variables were summarized using simple descriptive statistics. Qualitative / categorical variables were summarized by frequency counts and percentages. Two-sided 95% confidence intervals (CI) were calculated where mentioned.

Results

Participant flow and Recruitment

All participants who were eligible and signed the ICF were included in the final analysis for baseline characteristics and safety analysis. For the analysis of the primary and secondary endpoints, participants with an observation period of at least 6 months were included.



EFS: effectiveness data set; FVIII: coagulation factor VIII; FAS: full analysis set; ICF: informed consent form; LtFU: lost to follow-up; n: number of participants.
[a] Participants from Belgium (Data assessment was challenging and datasets were incomplete).
Source: DRM Minutes dated 13 Feb 2025; Table 1.1, Table 1.2

Baseline data

In total, 72 participants were enrolled. The participants were aged 20 months to 78 years. Participants were stratified by age at baseline; children < 12 years (n=8; males), adolescents (12 to 17 years; n=9; males) and adults (≤ 18 years; n=55; males). The median age was 30.5 years (range 20 months to 78 years) in total, 8.5 years (range 20 months to 10 years) in the pediatric group; 14.0 years (range 12 to 17) in the adolescent group and 36.0 years (range 18 to 78) in the adult group.

The distribution of mean (standard deviation) body weight (26.6 [10.81]; 61.6 [17.57]; 83.2 [15.18]), body mass index (16.5 [2.42]; 21.6 [5.23]; 25.5 [4.01]) and height (124.5 [24.42]; 167.7 [12.76]; 179.3 [8.03]) were consistent with the distribution of age in the pediatric-, adolescent-, and adult group, respectively. In the pediatric, adolescent, and adult group most subjects had severe hemophilia A (75.0%; 66.7%; 61.8%). Almost all participants (71/72) were PTPs.

Efficacy results

ABR / AsBR

The primary endpoints of this observational study were annualized bleeding rates (ABR) and annualized spontaneous bleeding rates (AsBR) for prophylaxis or on-demand treatment. Only bleeding episodes which required treatment were included in the analyses. Participants with a treatment period of less

than 12 weeks in a specific regimen were only evaluated under the "any prophylaxis" regimen, rather than being assessed within that specific regimen. The ABR and AsBR were presented by the effectiveness data set (EFS). In the EFS, most participants (54/61) received Afstyla for prophylaxis (7/7 children, 8/9 adolescents and 39/45 adults), whereas 11/61 participants received on demand treatment (2/7 children, 1/9 adolescents and 8/45 adults). The proportion of participants in the different prophylaxis dosing regimens was comparable (Table 1). Among the different age groups with a prophylaxis regimen, the highest median ABR was recorded for children, compared with adolescents and adults (ABR: 1.02 [range 0.0 to 1.7] vs. 0.65 [range 0.0 to 3.4] vs. 0.33 [range 0.0 to 9.0]). In participants with the comparable prophylaxis regimens, every second day and 3x weekly (= every 2.33 day), median ABRs were 0.74 (range 0.0 to 9.3) and 1.03 (range 0.0 to 4.5), respectively. The median ABRs for the 2x weekly and “other frequency” prophylaxis regimens were lower (each median ABR of 0, [range 0.0 to 3.0] and [range 0 to 5.1], respectively). For participants receiving on-demand treatment, the median ABR was 0.99 [range 0.0 to 20.1].

Table 1: Annualized Bleeding Rate with Regard to Treatment Regimen (EFS)

	Children < 12 years	Adolescents 12 to < 18 years	Adults ≥ 18 years	Total
	(N = 7)	(N = 9)	(N = 45)	(N = 61)
PROPHYLAXIS TREATMENT [a]	7	8	39	54
Any prophylaxis regimen: Total no. of bleeding episodes [b, c]				
n (missing)	7 (0)	8 (0)	39 (0)	54 (0)
Mean (SD)	2.43 (1.902)	2.63 (3.462)	4.15 (7.372)	3.70 (6.442)
Median	3.00	1.50	1.00	1.00
Min, Max	0.0, 5.0	0.0, 10.0	0.0, 25.0	0.0, 25.0
Any prophylaxis regimen: ABR [b, c]				
n (missing)	7 (0)	8 (0)	39 (0)	54 (0)
Mean (SD)	0.87 (0.674)	0.96 (1.190)	1.59 (2.598)	1.41 (2.274)
Median	1.02	0.65	0.33	0.57
Min, Max	0.0, 1.7	0.0, 3.4	0.0, 9.0	0.0, 9.0
95%-CI	0.27, 0.56	0.16, 0.82	0.41, 1.11	0.39, 0.90

	Children < 12 years	Adolescents 12 to < 18 years	Adults ≥ 18 years	Total
	(N = 7)	(N = 9)	(N = 45)	(N = 61)
Every second day regimen: Total no. of bleeding episodes [b]				
n (missing)	1 (0)	1 (0)	10 (0)	12 (0)
Mean (SD)	2.00 (-)	10.00 (-)	6.60 (10.233)	6.50 (9.415)
Median	2.00	10.00	1.00	2.00
Min, Max	2.0, 2.0	10.0, 10.0	0.0, 25.0	0.0, 25.0
Every second day regimen: ABR [b]				
n (missing)	1 (0)	1 (0)	10 (0)	12 (0)
Mean (SD)	0.72 (-)	3.37 (-)	2.85 (4.100)	2.71 (3.764)
Median	0.72	3.37	0.38	0.74
Min, Max	0.7, 0.7	3.4, 3.4	0.0, 9.3	0.0, 9.3
95%-CI	0.03, 2.62	0.39, 3.30	0.51, 3.33	0.51, 2.75
3x weekly regimen: Total no. of bleeding episodes [b]				
n (missing)	4 (0)	4 (0)	9 (0)	17 (0)
Mean (SD)	1.75 (2.062)	2.75 (1.708)	2.33 (3.873)	2.29 (2.995)
Median	1.50	2.50	1.00	2.00
Min, Max	0.0, 4.0	1.0, 5.0	0.0, 12.0	0.0, 12.0
3x weekly regimen: ABR [b]				
n (missing)	4 (0)	4 (0)	9 (0)	17 (0)
Mean (SD)	0.66 (0.767)	1.08 (0.655)	1.46 (1.707)	1.18 (1.328)
Median	0.59	0.95	1.15	1.03
Min, Max	0.0, 1.5	0.4, 2.0	0.0, 4.5	0.0, 4.5
95%-CI	0.16, 0.73	0.24, 0.77	0.24, 2.52	0.26, 1.30
2x weekly regimen: Total no. of bleeding episodes [b]				
n (missing)	2 (0)	2 (0)	11 (0)	15 (0)
Mean (SD)	3.00 (2.828)	0.00 (0.000)	1.18 (1.662)	1.27 (1.792)
Median	3.00	0.00	0.00	0.00
Min, Max	1.0, 5.0	0.0, 0.0	0.0, 5.0	0.0, 5.0
2x weekly regimen: ABR [b]				
n (missing)	2 (0)	2 (0)	11 (0)	15 (0)
Mean (SD)	1.61 (0.169)	0.00 (0.000)	0.55 (0.909)	0.62 (0.890)
Median	1.61	0.00	0.00	0.00
Min, Max	1.5, 1.7	0.0, 0.0	0.0, 3.0	0.0, 3.0
95%-CI	0.23, 3.58	NA	0.09, 0.77	0.11, 0.72

	Children < 12 years	Adolescents 12 to < 18 years	Adults ≥ 18 years	Total
	(N = 7)	(N = 9)	(N = 45)	(N = 61)
Other frequency regimen: Total no. of bleeding episodes [b, c]				
n (missing)	2 (0)	1 (0)	12 (0)	15 (0)
Mean (SD)	1.00 (1.414)	0.00 (-)	2.33 (3.892)	2.00 (3.546)
Median	1.00	0.00	0.00	0.00
Min, Max	0.0, 2.0	0.0, 0.0	0.0, 12.0	0.0, 12.0
Other frequency regimen: ABR [b, c]				
n (missing)	2 (0)	1 (0)	12 (0)	15 (0)
Mean (SD)	0.88 (1.251)	0.00 (-)	0.93 (1.624)	0.86 (1.497)
Median	0.88	0.00	0.00	0.00
Min, Max	0.0, 1.8	0.0, 0.0	0.0, 5.1	0.0, 5.1
95%-CI	0.31, 3.94	NA	0.20, 1.12	0.22, 1.01
ON-DEMAND TREATMENT [a]	2	2	8	12
On-demand regimen: Total no. of bleeding episodes [b]				
n (missing)	2 (0)	1 (1)	8 (0)	11 (1)
Mean (SD)	0.00 (0.000)	7.00 (-)	6.75 (13.477)	5.55 (11.605)
Median	0.00	7.00	2.50	2.00
Min, Max	0.0, 0.0	7.0, 7.0	0.0, 40.0	0.0, 40.0
On-demand regimen: ABR [b]				
n (missing)	2 (0)	1 (1)	8 (0)	11 (1)
Mean (SD)	0.00 (0.000)	2.57 (-)	3.31 (6.814)	2.64 (5.853)
Median	0.00	2.57	1.10	0.99
Min, Max	0.0, 0.0	2.6, 2.6	0.0, 20.1	0.0, 20.1
95%-CI	NA	0.28, 3.20	0.32, 6.86	0.31, 4.82

ABR: annualized bleeding rate; CI: confidence interval; EFS: effectiveness data set; Max: maximum; Min: minimum; N: total number of participants analyzed; n: number of participants; SD: standard deviation.
[a] Participants without any time on prophylaxis / on-demand treatment were excluded from the respective section.
[b] Participants with < 12 weeks on a specific regimen were set to missing in the analysis for that regimen. Only bleeding episodes requiring treatment were included.
[c] Any regimen included also the 'More frequently' regimen.
Source: Table 3.1

Assessor`s comment

Seven children were included in the EFS. Seven children received prophylaxis regimen according to the analysis of ABR. But two of these seven children were also treated on-demand. Regarding the footnote, any time on prophylaxis would exclude from on-demand section. The applicant should clarify.

Overall, the estimated ABRs are low, even for on-demand regimen, and are comparable to known ABR data of this product class.

With regards to spontaneous haemophilia-typical bleeding episodes, the median AsBR was 0 for most prophylaxis regimens (any prophylaxis regimen [range 0.0 to 7.7]) and on-demand regimen (range 0.0 to 2.0) across nearly all age groups. Median AsBRs was > 0 among adolescents with the 3x weekly prophylaxis regimen (median AsBR 0.17 [range 0.0 to 0.9]) and children with every second day prophylaxis regimen (median AsBR 0.72).

Haemostatic Effectiveness of Afstyla for the Treatment of Bleeding Episodes

For prophylaxis regimen, the vast majority of bleeding episodes (97.6%) required Afstyla treatment. Approximately half of the bleeding episodes (49.8%) were resolved with a single Afstyla infusion, 14.1% required 2 infusions and 33.7% needed more than 2 infusions. The median dose to treat a bleeding episode was 66 IU/kg (range 18.0 to 2708.0).

For on-demand treatment, the majority of bleeding episodes (98.4%) required Afstyla treatment. More than half of the bleeding episodes (59.7%) were resolved with a single Afstyla infusion, 17.7% required 2 infusions and 21.0% needed more than 2 infusions. The median dose to treat a bleeding episode was 24 IU/kg (range 21.0 to 321.0).

The haemostatic effectiveness of Afstyla was assessed by the investigators across visits, including the best and the worst ratings observed for each participant in the EFS. For most of the assessments (85.4%), the overall haemostatic effectiveness was rated as “excellent / good” and 6.3% of the assessments were rated as “moderate”. No haemostatic effectiveness was rated as “none”.

Assessor`s comment

No separate information has been provided on haemostatic effectiveness of Afstyla for the treatment of bleeding episodes in children and adolescents.

Afstyla Consumption

The median annualized Afstyla consumption for prophylaxis regimen was comparable in children (< 12 years) and adolescents (5478.75 IU/kg [range 2156.0 to 10,013.2] and 5626.59 IU/kg [range 3913.4 to 16,638.6], respectively) and lower for adults (4226.46 IU/kg [range 2035.0 to 14,610.0]).

The median annualized Afstyla consumption for on-demand treatment (1 adolescent and 7 adults) was 711 IU/kg and 182 IU/kg (range 100.0 to 1512.0), respectively.

Assessor`s comment

The higher consumption of Afstyla for prophylaxis in children and adolescents in comparison to adults could be explained with the need of higher protection due to physical activity and practising sport.

No further conclusion can be made from the consumption data for on-demand treatment due to the low evaluable number.

Characteristics of Bleeding Episodes

During prophylaxis treatment, 205 bleeding episodes were reported in total. Some of the bleeding episodes were reported in multiple locations simultaneously, resulting in a total of 219 recorded bleeding episodes in different locations. The most frequent bleeding locations were the ankle (21.5%), “other” location (19.2%), the knee (17.8%) and the elbow (16.9%). In descending frequency, the 205 bleeding episodes were “mild” (47.8%), “moderate” (27.8%) and “severe” (12.2%).

During on-demand treatment, 62 bleeding episodes were reported in total. Among 63 bleeding episodes recorded in different locations, the most frequent bleeding location was “other” location (49.2%). No bleeding episode was classified as severe; 59.7% were classified as “mild” and 17.7% as “moderate”.

Assessor`s comment

The characteristics of breakthrough bleeding during prophylaxis are mostly bleeds in the large joints. This observation is comparable to prophylaxis with other factor VIII products. But no differentiation between age groups has been made.

Frequency and Dosage of Afstyla Infusions

The median average prophylaxis interval for adolescents and adults was 2.33 days (range 2.0 to 3.5 and range 1.0 to 7.0) and for children was 2.67 days (range 2.0 to 7.0). Adolescents received the highest median average dose per infusion of 54 IU/kg (range 25.0 to 91.0), children received a median average dose per infusion of 43 IU/kg (range 32.0 to 59.0) and adults of 32.50 IU/kg (range 32.0 to 59.0).

In total, Afstyla was prescribed for prophylaxis in 86.0% of the cases, in 12.9% of the cases on demand and once (1.1%) for prevention in multiple surgeries. For all regimens, the prescription was longer than 12 weeks. During the study, 9.8% of the participants switched their regimen once and no one switched regimens twice or more. No details were available on the regimen switches.

Assessor`s comment

In general, Afstyla dosing frequency and dose per infusion administered during study conduct was largely in accordance with the recommendation in the SmPC (routine prophylaxis: adults and adolescents [≥ 12 years] 20 to 50 IU/kg administered 2 to 3x weekly; children [< 12 years] 30 to 50 IU/kg administered 2 to 3x weekly).

Safety results

In the FAS, in 25% of the participants a total of 29 AEs were reported, and 6 SAEs were reported in 8.3% of the participants (Table 21). One participant died of unknown reason. The death was assessed as not related to Afstyla. The reported PT was "Death", but the exact cause of death remained unknown as no autopsy was performed. The participant received a daily concomitant therapy with opioids during administration of Afstyla.

No participants were reported to develop inhibitors against FVIII under exposure to Afstyla. No adverse drug reactions (ADRs) or special situations were reported in this study.

Table 2: Overview of Number of Incidence of AEs (FAS)

	Total (N = 72)	
	n (%)	E (events)
AEs	18 (25.0%)	29
AEs classified as FVIII inhibitor formation	0	0
SAEs	6 (8.3%)	6
ADRs	0	0
Serious ADRs	0	0
AEs leading to death [a]	1 (1.4%)	1

ADR: adverse drug reaction; AE: adverse event; E (events): number of events; FAS: full analysis set; FVIII: coagulation factor VIII; N: total number of participants analyzed; n: number of participants experiencing an event; SAE: serious adverse event.
[a] Not related to Afstyla.
Source: Table 4.1

AEs were most frequently reported in the System Organ class (SOC) "Infections and Infestations" in 9.7% of the participants (7/2; 9 events). "Injury, Poisoning and Procedural Complications" in 8.3% of the participants (6/72; 8 events), "Gastrointestinal Disorders", and "Musculoskeletal and Connective Tissue Disorders" in 4.2% of the participants (3/72; 3 events each). AEs were largely non-serious, except for SOC "Gastrointestinal Disorders", where 2/3 AEs were serious (PT: Gastritis; Umbilical hernia).

Assessor`s comment

Since there were no FVIII inhibitor formation and no reporting of ADR, a differentiation of age groups is not required.

Overall, there were no new safety findings.

2.3.3. Discussion on clinical aspects

The aim of this non-interventional study NIS_PVA78092_CSL627 was to investigate the use of Afstyla under real-life conditions to confirm the effectiveness and safety of Afstyla established in the pivotal clinical studies in a broader haemophilia A population. Initially, it was planned to enrol 120 patients at approximately 50 haemophilia centres in the participating countries: Austria, Belgium, Czech Republic, Germany, Greece and Hungary. But only the number of 72 patients was reached despite the cautious statistical sample size calculation. Generally, the recruitment period was reduced in most of the participating countries. In Germany the main reason was the change of the "Vertriebsweg".

Overall, the estimated ABRs were low across different prophylactic treatment regimen, even for on-demand regimen. These results are in accordance with available ABR data of this product class. Seven children were included in the EFS and all of them received prophylaxis regimen. Two of these seven children were also treated on-demand after switching from prophylaxis to on-demand. Eight of 9 included adolescents received prophylaxis and two of these 9 adolescents on-demand.

There was a higher consumption of AFSTLA for prophylaxis in children and adolescents in comparison to adults which could be explained with the need of higher protection due to physical activity and practising sport. No further conclusion can be made from the consumption data for on-demand treatment due to the low evaluable number.

Regarding treatment of bleeding episodes, children < 12 years required more often >2 infusions and a higher total dose per bleeding episode than adolescents 12 to >18 years. This observation could be explained by the occurrence of more mild bleeding episodes in the group of adolescents.

The characteristics of breakthrough bleeding during prophylaxis were mostly bleeds in the large joints. This observation is comparable to prophylaxis with other factor VIII products. There was a difference in the involved location of bleeding episodes between children, adolescents and adults. But, due to the low number of children and adolescents investigated no further conclusions are possible.

In general, Afstyla dosing frequency and dose per infusion administered during study conduct was largely in accordance with the recommendation in the SmPC (routine prophylaxis: adults and adolescents [≥ 12 years] 20 to 50 IU/kg administered 2 to 3 x weekly; children [< 12 years] 30 to 50 IU/kg administered 2 to 3 x weekly).

Since there were no FVIII inhibitor formation and no reporting of ADR, a separate analysis of age groups is not required for the evaluation of safety. No new safety findings have been observed.

Overall, the conclusion of the applicant can be followed that Afstyla was safe and effective in preventing haemophilia-typic spontaneous bleeding episodes in most haemophilia A age groups and with nearly all Afstyla treatment regimens, either prophylaxis or on demand. No new safety signals were observed.

The provided data of real-world evidence show Afstyla treatment as prophylaxis and on demand to be effective with regards to ABR in participants with haemophilia A among all age groups. These results of the observational study are consistent with the previous clinical study program of Afstyla, demonstrating the effectiveness and safety of Afstyla in clinical practice and a broader haemophilia A population across Europe. Nevertheless, there are limitations on data interpretation due to the non-interventional design of the study and the large amount of missing data especially regarding PRO.

3. CHMP Rapporteur's overall conclusion and recommendation

Fullfilled, no further action required.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

1. The initially planned number of 120 patients was not reached. Since limited availability of patients was already regarded in the sample size calculation, the MAH should explain the reduced number of patients investigated.
2. Seven children were included in the EFS. These seven children received prophylaxis regimen according to the analysis of ABR. But two of these seven children were also treated on-demand. Regarding the footnote, any time on prophylaxis would exclude from on-demand section. The MAH should clarify.
3. No separate information has been provided on haemostatic effectiveness of Afstyla for the treatment of bleeding episodes in children and adolescents. The applicant should address.
4. Characteristics of bleeding episodes were not differentiated between age groups. The applicant should address.

The timetable is a 30-day response timetable without clock stop.

MAH responses to Request for supplementary information

1. The initially planned number of 120 patients was not reached. Since limited availability of patients was already regarded in the sample size calculation, the MAH should explain the reduced number of patients investigated.

Summary of MAH's Response:

Here a table for the planned and actual recruitment:

	Number of patients	
	planned per protocol	actual
BE	12	4
GR	12	12
CZ	4	2
DE	60	43
AT	20	9
HU	12	2

Here are the explanations for the different countries:

- **BE** -> the sites/country were closed prematurely in Oct 2021.
- **HU & CZ** -> both countries came in late but overall recruitment period was not prolonged.
- **DE/AT**-> Some sites did not start; COVID-19 (=> patients did not visit the sites) **DE:** § 47 AMG („Vertriebsweg – Faktor-Präparate") has been changed during time of enrollment, i.e. Afstyla could not be provided by the sponsor anymore but only by the pharmacies (thus, it was not necessary to visit the sites on a regular basis)

Assessment and Conclusion:

The applicant explained the reduced recruitment for the different involved countries. Generally, the recruitment period was reduced in most of the participating countries. In Germany the main reason was the change of the "Vertriebsweg". Thus, the smaller sample size has sufficiently been explained.

Issue resolved.

2. Seven children were included in the EFS. These seven children received prophylaxis regimen according to the analysis of ABR. But two of these seven children were also treated on-demand. Regarding the footnote, any time on prophylaxis would exclude from on-demand section. The MAH should clarify.

Summary of MAH's Response:

The two patients switched from a prophylaxis regimen to the on-Demand regimen On-demand ABR for these children only reflects on-demand period and prophylaxis ABR for these children only reflects prophylaxis period.

Assessment and Conclusion:

Both children were on the different treatment regimens on consecutive time periods and not at the same time.

Point resolved.

3. No separate information has been provided on haemostatic effectiveness of Afstyla for the treatment of bleeding episodes in children and adolescents. The MAH should address.

Summary of MAH's Response:

Please find in this table, the details on the haemostatic effectiveness of Afstyla for the treatment of bleeding episodes in children and adolescents.

Parameter	Children <12 years (N=7)	Adolescents 12 to <18 years (N=9)	Adults >=18 years (N=45)	Total (N=61)
-- PROPHYLAXIS TREATMENT ONLY [1] --	7	8	39	54
Total number of bleeding episodes	18 (100.0%)	21 (100.0%)	166 (100.0%)	205 (100.0%)
Total number of bleeding episodes requiring treatment	17 (94.4%)	21 (100.0%)	162 (97.6%)	200 (97.6%)
1 Infusion	6 (33.3%)	16 (76.2%)	80 (48.2%)	102 (49.8%)
2 Infusions	1 (5.6%)	0 (0.0%)	28 (16.9%)	29 (14.1%)
>2 Infusions	10 (55.6%)	5 (23.8%)	54 (32.5%)	69 (33.7%)
Total dose per bleeding episode requiring treatment (IU/kg) [2]				
n (missing)	17 (0)	21 (0)	162 (0)	200 (0)
Mean (SD)	257.12 (259.157)	118.57 (70.169)	133.64 (274.338)	142.55 (260.828)
Median	140.00	100.00	51.50	66.00
25%, 75%	67.00, 364.00	67.00, 100.00	38.00, 123.00	38.00, 133.50
Min, Max	18.0, 904.0	41.0, 304.0	24.0, 2708.0	18.0, 2708.0

Assessment and Conclusion:

The MAH provided the requested information on treatment of bleeding episodes. Children < 12 years required more often >2 infusions and a higher total dose per bleeding episode as adolescents 12 to >18 years. This observation could be explained by the occurrence of more mild bleeding episodes in the group of adolescents (see response to Q4).

Issue resolved.

4. Characteristics of bleeding episodes were not differentiated between age groups. The MAH should address.

Summary of MAH's Response:

Here is the information on the Characteristics of bleeding episodes with information on the age groups, data are split between on demand and prophylaxis treatment regimen.

-- PROPHYLAXIS TREATMENT ONLY [1] --	7	8	39	54
Total number of bleeding episodes	18	21	166	205
Number of bleeding episodes involving each location [2]	19 (100.0%)	23 (100.0%)	177 (100.0%)	219 (100.0%)
Ankle	6 (31.6%)	2 (8.7%)	39 (22.0%)	47 (21.5%)
Elbow	0 (0.0%)	0 (0.0%)	37 (20.9%)	37 (16.9%)
Epistaxis	0 (0.0%)	0 (0.0%)	4 (2.3%)	4 (1.8%)
Gastrointestinal	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hip	0 (0.0%)	0 (0.0%)	2 (1.1%)	2 (0.9%)
Intracranial	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Knee	1 (5.3%)	1 (4.3%)	37 (20.9%)	39 (17.8%)
Muscle	2 (10.5%)	0 (0.0%)	8 (4.5%)	10 (4.6%)
Organ	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other joint	0 (0.0%)	6 (26.1%)	6 (3.4%)	12 (5.5%)
Other location	3 (15.8%)	8 (34.8%)	31 (17.5%)	42 (19.2%)
Shoulder	0 (0.0%)	0 (0.0%)	5 (2.8%)	5 (2.3%)
Skin	1 (5.3%)	0 (0.0%)	0 (0.0%)	1 (0.5%)
Soft tissue	2 (10.5%)	1 (4.3%)	4 (2.3%)	7 (3.2%)
Wrist	0 (0.0%)	1 (4.3%)	2 (1.1%)	3 (1.4%)
missing	4 (21.1%)	4 (17.4%)	2 (1.1%)	10 (4.6%)
Maximal severity per bleeding episode [3]	18 (100.0%)	21 (100.0%)	166 (100.0%)	205 (100.0%)
mild	4 (22.2%)	12 (57.1%)	82 (49.4%)	98 (47.8%)
moderate	7 (38.9%)	4 (19.0%)	46 (27.7%)	57 (27.8%)
severe	1 (5.6%)	0 (0.0%)	24 (14.5%)	25 (12.2%)
missing	6 (33.3%)	5 (23.8%)	14 (8.4%)	25 (12.2%)

[1] Patient without any time on prophylaxis / on-demand are excluded from the respective section.
[2] Multiple answers are possible.
[3] Severity is defined as the maximal severity of all records belonging to one bleeding episode.
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Parameter	Children <12 years (N=7)	Adolescents 12 to <18 years (N=9)	Adults >=18 years (N=45)	Total (N=61)
-- ON-DEMAND TREATMENT ONLY [1] --	2	2	8	12
Total number of bleeding episodes	0	7	55	62
Number of bleeding episodes involving each location [2]	NA	7 (100.0%)	56 (100.0%)	63 (100.0%)
Ankle		0 (0.0%)	5 (8.9%)	5 (7.9%)
Elbow		0 (0.0%)	3 (5.4%)	3 (4.8%)
Epistaxis		0 (0.0%)	0 (0.0%)	0 (0.0%)
Gastrointestinal		0 (0.0%)	0 (0.0%)	0 (0.0%)
Hip		0 (0.0%)	0 (0.0%)	0 (0.0%)
Intracranial		0 (0.0%)	0 (0.0%)	0 (0.0%)
Knee		1 (14.3%)	4 (7.1%)	5 (7.9%)
Muscle		0 (0.0%)	6 (10.7%)	6 (9.5%)
Organ		0 (0.0%)	0 (0.0%)	0 (0.0%)
Other joint		2 (28.6%)	2 (3.6%)	4 (6.3%)
Other location		3 (42.9%)	28 (50.0%)	31 (49.2%)
Shoulder		0 (0.0%)	0 (0.0%)	0 (0.0%)
Skin		0 (0.0%)	0 (0.0%)	0 (0.0%)
Soft tissue		0 (0.0%)	3 (5.4%)	3 (4.8%)
Wrist		1 (14.3%)	3 (5.4%)	4 (6.3%)
missing		0 (0.0%)	2 (3.6%)	2 (3.2%)
Maximal severity per bleeding episode [3]	NA	7 (100.0%)	55 (100.0%)	62 (100.0%)
mild		1 (14.3%)	36 (65.5%)	37 (59.7%)
moderate		2 (28.6%)	9 (16.4%)	11 (17.7%)
severe		0 (0.0%)	0 (0.0%)	0 (0.0%)
missing		4 (57.1%)	10 (18.2%)	14 (22.6%)

[1] Patient without any time on prophylaxis / on-demand are excluded from the respective section.
[2] Multiple answers are possible.
[3] Severity is defined as the maximal severity of all records belonging to one bleeding episode.
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Assessment and Conclusion:

The MAH provided the requested information. There was a difference in the involved location and the severity per bleeding episodes between children and adolescents, which could explain the difference of required infusions and total dose per treatment. But, due to the low number of children and adolescents investigated no further conclusions are possible.

Issue resolved.