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Human Medicines Division

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

Advate

Octocog alfa

Procedure no: EMA/PAM/0000295686

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	**Description**	**Planned date**	**Actual Date**
☐	Submission deadline	30 September 2025	5 September 2025
☐	Start date	13 October 2025	13 October 2025
☐	CHMP Rapporteur AR	17 November 2025	17 November 2025
☐	CHMP comments	1 December 2025	N/A
☐	Updated CHMP Rapporteur AR	4 December 2025	N/A
☒	CHMP outcome	11 December 2025	11 December 2025

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1. Introduction

On 5 September 2025, the MAH submitted a completed paediatric study for ADVATE, 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 MACS-2025-022404 is a stand-alone study. The study is not part of the PIP or the clinical development program of ADVATE.

ADVATE was first approved in the United States in 2003. In Europe, ADVATE was registered on 02 March 2004 through a centralized procedure. In Europe, ADVATE is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) in all age groups.

2.2. Information on the pharmaceutical formulation used in the study

Octocog alfa (ADVATE) is a third-generation recombinant factor VIII (FVIII) concentrate developed by Baxter Healthcare Corporation (now part of Takeda). ADVATE is produced by recombinant DNA technology in the Chinese Hamster Ovary (CHO) cell line without the addition of any exogenous human- or animal-derived additives thereby eliminating the risk of potential contamination with viruses and/or prions. The product is provided as powder and solvent for solution for intravenous injection.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- MACS-2025-022404: Real-world Outcomes Among Non-Inhibitor Patients with Haemophilia A Treated with ADVATE vs. other Factor VIII in Combination or Concomitantly while Receiving Prophylaxis with Emicizumab.

The MAH declares that the results of this study do not require an update to the Product Information of ADVATE.

2.3.2. Clinical study

MACS-2025-022404: Real-world Outcomes Among Non-Inhibitor Patients with Haemophilia A Treated with ADVATE vs. other Factor VIII in Combination or Concomitantly while Receiving Prophylaxis with Emicizumab.

Description

MACS-2025-022404 was a non-interventional cohort study based on secondary closed claims data. The study aimed to describe and compare real-world clinical outcomes and healthcare costs for patients treated with ADVATE compared to other Factor VIII products in addition to emicizumab prophylaxis.

The United States of America (USA) was the only geographic region of interest. Data was obtained through HealthVerity from Inovalon, who owns the largest closed claims dataset sourced directly from 160+ USA payer plans across Medicare FFS & Advantage, Medicaid, and Commercial. The study was conducted with retroactive claims data from various medical points of service and pharmacy dispenses. Points of service included USA in-office, hospitals, and emergency rooms.

The patients were individuals who received emicizumab and recombinant FVIII treatment in medical and pharmaceutical settings within the USA during the study period from 01 February 2022 through 29 October 2024. The final analysis was completed on 30 March 2025. Start of patient follow-up was determined by the index date. The index date was the earliest emicizumab claim during the identification period. The end of follow-up was determined by the earlier of disenrollment, death, concomitant or concurrent treatment switch, emicizumab discontinuation, or end of study period. Confounding variables were identified in the baseline period (before the date of index treatment), while outcome/endpoint variables were defined during follow-up (after the date of index treatment).

The temporal anchors for the study were as follows:

- Data Extraction date, December 31st, 2024
- Source data range, March 1st, 2018 to October 29th, 2024
- Study period, February 1st, 2022 to October 29th, 2024
- Assessment window for inclusion and exclusion criteria, February 1st, 2022 to October 29th, 2024
- Window for identifying exposure, February 1st, 2023 to October 29th, 2024
- Follow-up window for observing outcome occurrence, from index date to final date of concurrent enrolment period, treatment class switch, death, end of study or emicizumab discontinuation.

Methods

Study participants

Inclusion criteria:

- Congenital haemophilia A (ICD-10-CM: D66) diagnosis during the study period
- At least one emicizumab claim after study period start
- At least 12 months continuous enrolment in database

Exclusion criteria:

Patients with a history of FVIII inhibitors or up to 2 claims at least 30 days apart for diagnoses of von Willebrand disease, haemophilia B, acquired haemophilia A or acquired coagulation factor deficiency during the 12-month baseline period.

Evidence of FVIII inhibitors was defined as at least 1 claim for bypass therapies (FEIBA, NOVOSEVEN, SEVENFACT), rituximab, or evidence of immune tolerance induction therapy during the 12-month baseline period. Immune tolerance induction therapy was defined as the presence of a claim for the Bethesda/Nijmegen assay during the baseline period and a high dose of Factor VIII therapy (>3 times

the median IU dispensed for patients in the same age group over five consecutive 28-day periods) during the baseline period.

Treatments

Treatments were only recorded based on pharmacy claims.

Objective(s)

Primary objective 1 – Describe real-world patients with non-inhibitor haemophilia A on emicizumab prophylaxis treated with concurrent or concomitant use of ADVATE vs other Factor FVIII in terms of demographic and clinical characteristics.

Primary objective 2 – Among emicizumab patients, quantify and compare the health care resource utilization (HCRU), pharmacy costs and annualized bleeding rate (ABR) associated with concurrent or concomitant use of ADVATE compared to other FVIII products.

Secondary objective 1 – Describe treatment patterns of non-inhibitor haemophilia A emicizumab patients

Outcomes/endpoints

Primary Outcome Variables

- Billed Annualized bleeding rate (ABR)
    - ABR is defined as the annualized rate of bleeding codes captured during the follow-up period. These codes have been reviewed and confirmed with the medical review team. All bleeding codes (both inpatient and outpatient) were grouped based on the body part where the bleeding event occurred. Multiple bleeding claims for the same body part around a 7-day window were grouped together as 1 bleeding event. If multiple claims for bleeds occurred in different body parts, with or without the 7-day window, they were treated as separate claims.
    - Patients with bleeding (events stratified by major and minor, as defined by ICD diagnosis codes and site of bleeding).
- Health Care Resource Utilization and Cost (Annualized)
    - Inpatient Visits
    - Outpatient Visits
    - Emergency Room Visits
    - Factor VIII Utilization
    - Calculated Pharmacy Cost (sum of dispensed units per treatment per patient multiplied by each treatment's Average Sales Price (ASP) per unit).

Secondary Outcome Variables

- Treatment patterns
    - Emicizumab Discontinuation: A gap of at least 90 days between prescriptions of emicizumab therapy. The last day of supply before the gap will be identified as the discontinuation date.
    - Switch: The presence of a class switch of Factor VIII replacement in a concomitant or concurrent usage pattern. Both time to switch and number of switches will be explored.

Sample size

During the feasibility stage of the analysis, 1,282 patients meeting the study's entry criteria were identified.

Randomisation and blinding (masking)

Not applicable

Statistical Methods

Propensity score weighting was implemented to improve balance between the concurrent FVIII cohorts. Multivariable analysis used covariates with adequate frequency (n occurrences > 14 across ADVATE and comparator cohorts) and correlation (Pearson correlation <= 0.8) to calculate propensity scores. Normalized inverse probability of treatment weighting (IPTW) weights were calculated using propensity scores. To limit the impact of extreme weights, these were truncated to the first and 99th percentile. Standardized mean differences (SMDs) were assessed for each cohort to confirm that IPTW adequately balanced confounders. Finally, an outcome analysis with the matched groups determined if the difference in outcomes was significant via a weighted paired t-test, weighted multivariate Poisson regression, or weighted multivariate Gaussian regression.

Results

Recruitment and numbers analysed

1,282 (4.03%) of a total of 31,800 patients with a diagnosis of congenital haemophilia A met the study's entry criteria (i.e. emicizumab use, absence of FVIII inhibitors and an at least 12 months continuous enrolment in the database). A total of 633 of these had additional FVIII pharmacy claims within the study period. These included 274 patients with claims for ADVATE, 132 patients with claims for alternative standard half-life (SHL) FVIII products, and 227 patients with claims for extended half-life (EHL) FVIII agents. A sub-cohort of EHL patients who received exclusively Altuviiio (n=31) was also described but the sample size was too small for multivariate comparison.

Baseline data

Demographics and other baseline characteristics are summarized in **Table 1**.

Patients in the ADVATE cohort had an average age of 20 years (median = 17 years). There were 8 (2.9%) patients aged <6 years, 62 (22.6%) patients aged 6 to 11 years, 70 (25.5%) patients aged 12 to 17 years, and 134 (48.9%) patients aged ≥18 years. The patients primarily had Medicaid coverage (69.7%) and had a roughly equal distribution of residence across the United States.

Baseline characteristics were generally balanced across the different FVIII cohorts. However, the ADVATE cohort was approximately 3 to 6 years younger than the other cohorts. All cohorts included almost exclusively male patients (>98%). Regions of residence varied significantly across the cohorts, with differences of up to 30%.

Table 1. Demographic and baseline characteristics of study participants

		Patients with emicizumab prophylaxis				
		All patients	With FVIII concomitant or concurrent use			
			Advate	SHL	EHL	Exclusively Altuviiio
n		1282	274	132	227	31
Age at index, mean (SD)		23.02 (13.8)	20.16 (12.1)	26.43 (13.6)	22.8 (12.5)	23.55 (12.7)
Age at index, median (IQR)		19.0 (18.0)	17.0 (14.0)	24.5 (18.2)	20.0 (15.5)	17.0 (23.0)
Age, n (%)	< 6	39 (3.0%)	8 (2.9%)	5 (3.8%)	5 (2.2%)	1 (3.2%)
	6 - 11	239 (18.6%)	62 (22.6%)	16 (12.1%)	33 (14.5%)	4 (12.9%)
	12 - 17	264 (20.6%)	70 (25.5%)	11 (8.3%)	56 (24.7%)	11 (35.5%)
	18+	740 (57.7%)	134 (48.9%)	100 (75.8%)	133 (58.6%)	15 (48.4%)
	Unknown/missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Gender, n (%)	Male	1268 (98.9%)	272 (99.3%)	131 (99.2%)	224 (98.7%)	31 (100.0%)
	Female	14 (1.1%)	2 (0.7%)	1 (0.8%)	3 (1.3%)	0 (0.0%)
	Unknown/missing	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Index year, n (%)	2023	1212 (94.5%)	263 (96.0%)	123 (93.2%)	222 (97.8%)	30 (96.8%)
	2024	70 (5.5%)	11 (4.0%)	9 (6.8%)	5 (2.2%)	1 (3.2%)

The medical history of patients with emicizumab prophylaxis during the baseline period indicates 9.8% of emicizumab patients had a cardiovascular comorbidity, 87% of which was hypertension. Additionally, 9.3% had a minor bleeding diagnosis during baseline, 1.2% a major bleeding event, and 34% had another significant diagnosis of interest.

Medical history and clinical characteristics were less well balanced across the cohorts. ADVATE patients appeared the least comorbid, with fewer metabolic conditions (7%), cardiovascular conditions (5%), and patients with a Charlson comorbidity index (CCI) greater than 1 (6%). SHL patients most often had a CCI greater than 1 (11%), with the highest average among cohorts of 0.5. EHL patients had the lowest incidence of bleed diagnoses in the baseline period (9%), while the Altuviiio sub-cohort had the highest incidence of 19%.

Efficacy results

HCRU, Pharmacy Costs and ABR

Propensity score weighting was implemented to improve balance between the concurrent FVIII cohorts. The comparison of concurrent ADVATE use to other SHL FVIII agents did not reveal significant differences. Both the unadjusted and adjusted comparisons showed no difference in clinical outcomes, HCRU outcomes or costs.

Adjusted multivariate analysis showed that ADVATE for concomitant or concurrent use in addition to emicizumab prophylaxis was associated with lower associated pharmacy costs compared to concomitant or concurrent use of EHL agents. The average difference in annualized pharmacy costs was $28,000 (95% CI: [$15,000, $41,000]) in the unadjusted analysis and $25,000 (95% CI: [$12,000, $38,000]) in the adjusted analysis (both statistically significant, p-value < 0.005).

The adjusted annualized mean number of inpatient visits among patients with ADVATE use (0.16) was higher than among patients with EHL use (0.05, p-value = 0.03). However, both ABR and the annualized average cost of medical care were not significantly different between the 2 groups.

Age Stratified Analysis

Patient age was grouped into 4 categories: <6, 6-11, 12-17, and 18+. Descriptive outcomes of means among paediatric patients revealed few comparisons of statistical significance with adequate sample sizes. Among patients less than 6 years old, no significant differences were observed (**Table 2**). For those aged 6-12 years, a significant difference was observed only between the ADVATE (n=62) and Altuviiio (n=4) cohorts (**Table 3**). Among the subgroup of adolescents aged 12–18 years, ADVATE users had significantly lower pharmacy costs compared to EHL users ($26,662 vs. $53,911; p = 0.01), with no significant differences in ABR or inpatient visits (**Table 4**).

Table 2. Comparison of Outcome Means Among Infants and Young Children (Age 0-5.9 years)

	Advate (n=8)	SHL (n=5)	p-value	EHL (n=5)	p-value	Altuviiio (n=1)	p-value
ABR, mean [95% CI]	0.63 [0.39, 0.86]	0.00 [0.00, 0.00]	0.08	0.54 [0.21, 0.86]	0.89	2.7	-
ER Visits, annualized mean [95% CI]	1.03 [0.68, 1.38]	1.39 [0.92, 1.87]	0.70	0.46 [0.29, 0.64]	0.31	0	-
Inpatient Visits, annualized mean [95% CI]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	-	0.00 [0.00, 0.00]	-	0	-
Outpatient Visits, annualized mean [95% CI]	25.53 [14.98, 36.09]	8.91 [6.43, 11.39]	0.28	52.32 [32.50, 72.14]	0.48	171.16	-
Calculated Pharmacy cost ($), mean [95% CI]	5009.11 [4160.08, 5858.14]	10776.02 [6952.92, 14599.11]	0.41	15037.56 [10458.88, 19616.24]	0.26	9198.45	-
FVIII Utilization, annualized mean [95% CI]	2.04 [1.64, 2.43]	3.87 [2.68, 5.06]	0.41	1.72 [1.41, 2.03]	0.67	1.08	-
Annualized Thrombotic Events (TE) in follow-up, mean [95% CI]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	-	0.00 [0.00, 0.00]	-	0	-
Procedural Total Cost of Care ($), annualized mean [95% CI]	3396.95 [2080.73, 4713.17]	4134.41 [2796.16, 5472.66]	0.80	2450.89 [1632.05, 3269.73]	0.67	1488.59	-
Medical Claims Total Cost of Care ($), annualized mean [95% CI]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	-	0.00 [0.00, 0.00]	-	0	-

Table 3. Comparison of Outcome Means Among Children (Age 6-11.9 years)

	Advate (n=62)	SHL (n=16)	p-value	EHL (n=33)	p-value	Altuviiio (n=4)	p-value
ABR, mean [95% CI]	0.34 [0.13, 0.54]	0.18 [0.08, 0.27]	0.21	0.29 [0.09, 0.49]	0.78	0.00 [0.0, 0.0]	**0.00**
ER Visits, annualized mean [95% CI]	0.69 [0.41, 0.98]	0.47 [0.22, 0.72]	0.40	0.90 [0.52, 1.28]	0.47	0.15 [-0.14, 0.43]	**0.02**
Inpatient Visits, annualized mean [95% CI]	0.11 [0.01, 0.20]	0.11 [0.02, 0.20]	0.96	0.02 [-0.01, 0.04]	0.06	0.00 [0.0, 0.0]	**0.02**
Outpatient Visits, annualized mean [95% CI]	18.40 [9.60, 27.20]	11.19 [7.73, 14.66]	0.17	15.13 [7.25, 23.00]	0.62	6.03 [4.14, 7.93]	**0.00**
Calculated Pharmacy cost ($), mean [95% CI]	10323.34 [6821.76, 13824.93]	13699.51 [9555.99, 17843.03]	0.42	24935.65 [12450.62, 37420.69]	0.08	45494.75 [-5626.63, 96616.12]	0.27
FVIII Utilization, annualized mean [95% CI]	1.81 [1.47, 2.14]	2.28 [1.93, 2.63]	0.20	2.25 [1.68, 2.82]	0.27	1.87 [0.83, 2.91]	0.92
Annualized Thrombotic Events (TE) in follow-up, mean [95% CI]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]	-	0.00 [0.00, 0.00]	-	0.00 [0.0, 0.0]	-
Procedural Total Cost of Care ($), annualized mean [95% CI]	2421.33 [1520.59, 3322.08]	1563.42 [1031.79, 2095.05]	0.19	2459.04 [1716.27, 3201.82]	0.95	1218.83 [686.02, 1751.63]	**0.02**
Medical Claims Total Cost of Care ($), annualized mean [95% CI]	5396.36 [-271.78, 11064.49]	11038.65 [780.33, 21296.98]	0.57	253.03 [-138.30, 644.35]	0.06	0.00 [0.0, 0.0]	**0.05**

Table 4. Comparison of Outcome Means Among Adolescents (Age 12-18 years)

	Advate (n=70)	SHL (n=11)	p-value	EHL (n=56)	p-value	Altuviiio (n=11)	p-value
ABR, mean [95% CI]	0.36 [0.09, 0.63]	0.20 [0.02, 0.38]	0.50	0.33 [0.13, 0.53]	0.87	0.78 [0.02, 1.53]	0.32
ER Visits, annualized mean [95% CI]	0.73 [0.31, 1.15]	0.30 [0.16, 0.43]	0.08	0.44 [0.18, 0.70]	0.19	0.38 [-0.37,1.13]	0.42
Inpatient Visits, annualized mean [95% CI]	0.25 [-0.04, 0.54]	0.15 [0.01, 0.28]	0.62	0.05 [-0.02, 0.13]	0.15	0.22 [-0.11, 0.54]	0.88
Outpatient Visits, annualized mean [95% CI]	12.97 [8.11, 17.83]	9.20 [7.24, 11.16]	0.22	16.07 [4.54, 27.59]	0.61	15.72 [9.37, 22.07]	0.49
Calculated Pharmacy cost ($), mean [95% CI]	26662.11 [15608.07, 37716.14]	14753.55 [11839.63, 17667.48]	**0.05**	53911.15 [35673.55, 72148.74]	**0.01**	120991.97 [53498.39, 188485.55]	**0.02**
FVIII Utilization, annualized mean [95% CI]	2.19 [1.62, 2.76]	1.40 [1.23, 1.58]	**0.02**	2.57 [2.04, 3.10]	0.30	3.54 [2.03, 5.05]	0.12
Annualized Thrombotic Events (TE) in follow-up, mean [95% CI]	0.00 [0.00, 0.00]	0.00 [0.00, 0.00]		0.00 [0.00, 0.00]		0.00 [0.0, 0.0]	
Procedural Total Cost of Care ($), annualized mean [95% CI]	14270.57 [-153.97, 28695.11]	1377.48 [1095.71, 1659.26]	**0.05**	15615.05 [1115.42, 30114.67]	0.89	66933.63 [2523.78, 131343.48]	0.14
Medical Claims Total Cost of Care ($), annualized mean [95% CI]	22079.65 [-7811.26, 51970.56]	6130.75 [604.07, 11657.43]	0.27	3166.78 [-1109.36, 7442.91]	0.16	12993.40 [-6955.58, 32942.38]	0.59

Safety results

Not applicable.

2.3.3. Discussion on clinical aspects

As part of this Article 46 procedure, the MAH submitted the study report of MACS-2025-022404 together with a clinical overview addendum.

MACS-2025-022404 was a non-interventional retrospective cohort study based on closed claims data from the US healthcare system. The study aimed to describe and compare real-world clinical outcomes and healthcare costs for non-inhibitor patients with haemophilia A, who receive treatment with ADVATE or alternative Factor VIII products in addition to background emicizumab prophylaxis.

Data was obtained through HealthVerity from Inovalon, who owns the largest closed claims dataset sourced directly from 160+ USA payer plans, and was collected between 01 February 2022 and 29 October 2024 (study period), with source data ranging from 01 March 2018 to 29 October 2024.

Inclusion criteria required patients to have i) a confirmed diagnosis of congenital haemophilia A, ii) at least one emicizumab claim within the study period and iii) a minimum of 12 months of continuous enrolment in the database. Patients were excluded if they had a history of FVIII inhibitors, or if they had up to 2 claims by at least 30 days apart for diagnoses such as von Willebrand disease, haemophilia B, acquired haemophilia A, or acquired coagulation factor deficiency during the 12-month baseline period.

The study analysed real-world outcomes, including bleeding events, healthcare resource utilisation (HCRU) and Factor VIII pharmacy claims, for a total of 633 patients. Of these, 274 patients had claims

for ADVATE, 132 for other standard half-life (SHL) FVIII agents and 227 for extended half-life (EHL) FVIII products.

The ADVATE cohort included 140 (51.1%) patients <18 years of age. These included 8 (2.9%) children aged <6 years, 62 (22.6%) children aged 6 to 11 years, and 70 (25.5%) adolescents aged 12 to 17 years.

In essence, results of study MACS-2025-022404 indicate that for patients with inhibitor-negative haemophilia A on emicizumab prophylaxis in the US, ADVATE was the most commonly used concomitant FVIII agent. In addition, comparisons of the different FVIII subgroups (ADVATE vs. other SHL products and ADVATE vs. EHL products) suggest that despite similar clinical outcomes and total costs, concurrent use of ADVATE instead of EHL products alongside emicizumab prophylaxis results in lower pharmacy costs, with an average annual difference of approximately $25,000 per patient (adjusted multivariate analysis). In contrast, the comparison of concurrent use of ADVATE to alternative SHL agents did not reveal any significant differences.

Descriptive outcomes of means among the paediatric subsets of the study population revealed few comparisons of statistical significance. However, many of the comparisons were affected by considerable differences in sample size, with generally few patients under 6 years of age and a much lower number of patients using other SHL agents compared to ADVATE or EHL products. However, the comparison of adolescents who received ADVATE (n=70) with those who received EHL products (n=56) also revealed significantly lower pharmacy costs in the ADVATE cohort, with no significant differences observed in ABR or inpatient visits.

Overall, the newly submitted RWE study provides insights into the concomitant use of FVIII products and outcomes in patients with inhibitor-negative congenital haemophilia A receiving emicizumab prophylaxis in the US. In relation to the US, the study sample appears to be generally representative of haemophilia A patients receiving emicizumab prophylaxis. However, given the anticipated fundamental differences in the respective healthcare systems and reimbursement structures, transferability and relevance of the reported outcomes to Europe and/or individual European countries remains limited.

Furthermore, the interpretation of the reported outcomes is hampered by the inherent limitations of retrospective observational studies, as well as limitations in sample size. Statistical comparisons were often affected by considerable differences in cohort sizes, which were particularly pronounced in the subgroup of children. In addition, information about treatments was limited to pharmacy claims without further information about the actually administered doses or the effectiveness of treatment.

The study did not evaluate treatment-emergent adverse events. However, an apparent absence of thrombotic events in the paediatric subset of patients (captured as the outcome of "Annualized thrombotic events in follow-up") is acknowledged.

In summary, it is agreed with the MAH that the results of study MACS-2025-022404 do not change the benefit-risk profile for ADVATE and that no updates of its product information are required.

3. Rapporteur's overall conclusion and recommendation

Final data of study MACS-2025-022404 do not change the favourable benefit risk profile of ADVATE in its approved indication. The submitted data do not warrant any update of its Product information, and no regulatory actions are required.

☒ **Fulfilled:**

No regulatory action required.