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

Advate

Octocog alfa

Procedure no: EMEA/H/C/000520/P46/104

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**	**Need for discussion**
☐	Start of procedure	24 Jun 2024	24 Jun 2024	☐
☐	CHMP Rapporteur Assessment Report	29 Jul 2024	24 Jul 2024	☐
☐	CHMP members comments	12 Aug 2024	12 Aug 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	16 Aug 2024	16 Aug 2024	☐
☐	Request for Supplementary Information	22 Aug 2024	22 Aug 2024	☐
	Submission	15 Oct 2024	15 Oct 2024	
☐	Re-start	16 Oct 2024	16 Oct 2024	☐
☐	CHMP Rapporteur Assessment Report	30 Oct 2024	30 Oct 2024	☐
☐	CHMP members comments	04 Nov 2024	04 Nov 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	07 Nov 2024	07 Nov 2024	☐
☒	CHMP adoption of conclusions	14 Nov 2024	14 Nov 2024	☐

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1. Introduction

On 23th May 2024, the MAH submitted a completed paediatric study for Advate, in accordance with Article 46 of Regulation (EC) No 1901/2006, 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-2020-051901 is a stand-alone study.

The MAH stated that study MACS-2020-051901 is not part of the PIP or the clinical development program of Advate.

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.

Advate was first approved in the United States (US) in 2003. In Europe, Advate was registered on 02 March 2004 through a centralized procedure. As of 31 December 2023, Advate is approved in 71 countries worldwide. In the EU, Advate is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) in all age groups.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- MACS-2020-051901: Local, multicenter, non-interventional, ambispective study in severe Hemophilia A patients on standard and PK-tailored prophylaxis with octocog alfa (Advate) in the Russian Federation (HAPKIDO)

Study MACS-2020-051901 was designed to identify changes in FVIII trough levels in patients who had been upgraded from standard prophylaxis with Advate to individualized prophylaxis based on PK assessments using myPKFiT in common practice. MyPKFiT, a CE-marked medical device, is an online medical application that allows authorized users to simulate dosing regimens for Advate with patient pharmacokinetic profiles based on only 2 blood samples (the first between 3-4 hours ± 30 minutes and the second between 24-32 hours ± 1 hour post infusion). Since 2018, approximately 50 clinics all over Russia are using myPKFiT in their routine clinical practice.

The study was conducted in Russian male patients of all ages with severe haemophilia A (FVIII < 1%) or moderate haemophilia A with severe bleeding phenotype.

According to the MAH, results of study MACS-2020-051901 do not require an update of the Advate Product Information.

2.3.2. Clinical study

MACS-2020-051901: Local, multicenter, non-interventional, ambispective study in severe Haemophilia A patients on standard and PK-tailored prophylaxis with octocog alfa (Advate) in the Russian Federation (HAPKIDO)

Description

Study MACS-2020-051901 (TAK-761-4001; HAPKIDO) was a local, multicenter, non-interventional ambispective study conducted to identify changes in FVIII trough levels in severe haemophilia patients who had been upgraded from standard prophylaxis with octocog alfa to individualized PK-guided prophylaxis with myPKFiT and to analyse differences in clinical outcomes before and after implementation of PK-guided treatment.

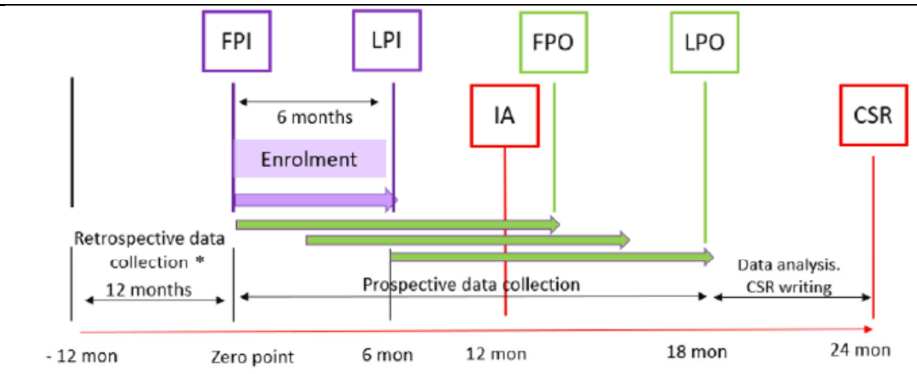
The study was conducted from 18 August 2021 (first patient inclusion) to 04 April 2023 (last patient last visit) in 13 clinical sites across 13 cities of Russia.

The study used secondary data (retrospective data collection at baseline) and primary data (data obtained from the patients' follow-up during the study) collections obtained in routine clinical practice from the following data sources:

- patients' medical charts;
- each patient had PK measurements and FVIII infusions (frequency/dosing) recorded;
- FVIII activity – laboratory data records;
- all the PK curves and corresponding tables stored as pdf files in myPKFiT program;
- bleeding rate (data will be taken from out-patients' medical charts).

During the prospective part of the study, data were collected from 3 visits: Visit 1 (baseline), Visit 2 (Month 6), and Visit 3 (Month 12 or early discontinuation). At the baseline visit, the retrospective data were collected for patients who had been on standard prophylaxis or PK-tailored prophylaxis with octocog alfa during 12 months prior to the study enrollment.

Figure 1: Study design



CSR=Clinical Study Report; FPI=first patient in; FPO=first patient out; IA=interim analysis; LPI=last patient in; LPO=last patient out; Zero point=start patient's enrollment

*Retrospective data collection only for patients who had been on standard prophylaxis or PK-tailored prophylaxis with octocog alfa during 12 months prior to the study enrollment.

Source: Figure 1_clincial study report

Methods

Study participants

Inclusion criteria:

- Male patients of all ages with severe haemophilia A (FVIII < 1%) or moderate haemophilia A with severe bleeding phenotype who:
  - had been on standard prophylaxis or PK-tailored prophylaxis with octocog alfa during at least 12 months prior to the study enrollment (150 patients) or who started octocog alfa (Advate) treatment in 2021 (20 patients),
  - is being treated with octocog alfa at the moment of enrolment with any of the abovementioned treatment modalities, and
  - had been assigned octocog alfa provision in Federal reimbursement program 2021,
  - have individual data of octocog alfa (Advate) half-life ($T_{1/2}$) from myPKFiT application.
- Availability of patients' records sufficient for data collection according to the study objectives during the retrospective period of the study for patients who had been on standard prophylaxis or PK-tailored prophylaxis with octocog alfa during at least 12 months prior to the study enrollment.
- Written informed consent provided by the patient or, in case of children below 18 years of age, by patient's parent or patient's legally acceptable representative.

Exclusion criteria

- Failure to obtain the patient's written informed consent.
- Participation in any interventional study of products for hemophilia or other hemostasis disturbances treatment during 12 months prior to the study enrollment for patients who has retrospective data collection period and during 12 months after the study enrollment for all patients.

Treatments

Treatment decisions were made by the attending physicians. Treatment of interest was octocog alfa (Advate). Octocog alfa (Advate) should have been administered according to the official prescribing information (the Russian packaging leaflet). The study medication was not provided by the Sponsor.

Outcomes/endpoints

Primary outcome:

- the time per week spent with the trough FVIII level below 1% on the standard prophylaxis and after PK-tailoring.

Secondary outcomes:

- proportion/percentage of patients with more than 19 hours per week spent with FVIII trough level below 1% on standard prophylaxis vs on PK-tailored prophylaxis;
- proportion of patients with upgraded dosing regimen based on PK-assessment, with upgrades specified (dose upgrade, dosing intervals modification, and/or FVIII trough level upgrade to above 1%);

- proportion of patients with time per week spent with FVIII trough level below 1%, 1- <3%, and ≥3% while on standard and individualized prophylaxis;
- proportion/percentage of patients with FVIII trough level permanently above 1% on standard prophylaxis vs on PK-tailored prophylaxis;
- correlation between the time per week spent with FVIII trough level below 1% and spontaneous ABR and AJBR on standard prophylaxis;
- correlation between the time per week spent with FVIII trough level below 1%, 1- <3% and ≥3% and ABR and AJBR on PK-tailored prophylaxis;
- FVIII annualized consumption before and after PK-tailoring, in patients in whom the dosage regimen had been adjusted;
- proportion of patients with positive dynamics of BMI due to increased physical activity after transfer from standard to individualized prophylaxis;
- proportion of patients using healthcare resources due to insufficient bleeding control before and after PK-tailoring (healthcare resources include hospitalizations and days away from work or school/institute).

Sample size

Sample size was calculated for the primary endpoint "the time per week spent with the trough FVIII level below 1% on the standard prophylaxis and after PK-tailoring". Under the assumption of a 15% change of annual bleed rate being a clinically relevant difference and a 1.4% increase in the annual bleed rate for each additional hour of FVIII below 1% (cf. Collins et al., 2009), the sample size was calculated for a minimal detectable difference in mean time per week spent with the trough FVIII level below 1% of 10 hours (and a standard deviation of no more than 20 hours). With a two-sided Type I error of 0.05 and an analysis power of 80%, the calculated minimum sample size required to assess time per week spent with a trough FVIII level below 1% was no less than 63 patients.

In order to address the uncertainty related to the expected variance of the estimate and to allow for subgroup analysis, the planned number of patients to be included into the study was approximately 170 (including 20 patients newly treated with octocog alfa). However, due to a lower than expected enrolment rate, the Sponsor decided to stop patients' enrollment on 24 March 2022, when 94 patients had been enrolled and completed the study.

Randomisation and blinding (masking)

Not applicable. Study MACS-2020-051901 was an observational study.

Statistical Methods

The statistical analysis involved the Full Analysis Set (FAS) that included all the patients enrolled in the study.

A descriptive analysis approach was used to analyse the data and the study outcomes for the different study subgroups.

Statistical tests were two-sided with 5% confidence level. For comparative analysis of continuous variables, Wilcoxon signed-rank test or Kruskal Wallis test was applied. For comparison of categorical measures, Fisher exact test was used.

Correlation analysis was performed using Pearson and Spearman correlation coefficients.

All outcomes of interest were analysed in the following subgroups:

- all time on PK-tailored prophylaxis;
- all time on standard prophylaxis;
- shifted from standard to PK-tailored prophylaxis on Visit 2;
- shifted from standard to PK-tailored prophylaxis on Visit 3.

Results

Recruitment / Participant flow / Numbers analysed

A total of 94 male patients with severe (or moderate with severe bleeding phenotype) haemophilia A were enrolled and completed the study. There were no drop-outs during the study. Based on PK assessment using myPKFiT at the Visit 1 (baseline), 59 (62.8%) patients received standard prophylaxis and 35 (37.2%) patients received individualized PK-tailored prophylaxis. After baseline, a total of 21 (22.3%) patients were shifted from standard prophylaxis to PK-tailored prophylaxis during the study.

Table 1: Disposition of Patients and Subgroups

Variable	Value	Number of Subjects / Descriptive Statistics – Analysis population (N=94)
Therapy regimen after myPKFiT	Patients on standard prophylaxis	59 (62.77%)
	Patients on PK-tailored prophylaxis	35 (37.23%)
Shifted from standard prophylaxis to PK-tailoring prophylaxis, Visit 2	No	75 (79.79%)
	Yes	19 (20.21%)
Shifted from standard prophylaxis to PK-tailoring prophylaxis, Visit 3	No	92 (97.87%)
	Yes	2 (2.13%)
Shifted from standard prophylaxis to PK-tailoring prophylaxis	No	73 (77.66%)
	Yes	21 (22.34%)

Source: Excerpt of Table 3_clincial study report

Baseline data

Demographics: The study population consisted mostly of paediatric patients (83 (88.3%) patients <18 years old at enrollment); the remaining patients were adults (11 patients ≥18 years old at enrollment). The mean (standard deviation [SD]) age of the patients was 12.6 (8.2) years (range: 1–48 years). All study patients were male.

Physical activity: Twelve (12.8%) patients had high physical activity level, 76 (80.9%) patients had moderate physical activity, and 6 (6.4%) patients had low physical activity level.

Prophylaxis regimen: At baseline, 59 (62.8%) patients were on standard prophylaxis and 35 (37.2%) patients were on the individualized PK-tailored prophylaxis of bleeding; 41 (43.6%) patients were using the myPKFiT mobile application.

Pharmacokinetics Parameters Obtained from myPKFiT Assessment: The mean (SD) of FVIII clearance was 0.0 (0.0) dL/h/kg; the mean (SD) of FVIII $t_{1/2}$ was 10.1 (1.6) hours; the mean (SD) of steady-state volume of distribution was 0.6 (0.1) dL/kg. The mean (SD) time when FVIII was above 1% of initial level was 56.2 (10.1) hours.

Assessor's comment:

The mean (SD) FVIII clearance of 0.0 (0.0) dL/h/kg collected at baseline is considered remarkable and should be further explained / critically discussed.

Bleeding rate during 12 months before inclusion: 75 patients had available data on haemorrhages during 12 months before inclusion. Among these, the mean (SD) number of haemorrhages during 12 months before inclusion was 1.7 (2.0), ranging from 0 to 8 haemorrhages per patient.

Arthropathic status evaluation showed that 37/94 (39.4%) patients had arthropathic joints. The mean (SD) number of arthropathic joints per patient was 1.9 (1.4) ranging from 1 to 7 arthropathic joints per patient. 37/94 (39.4%) patients had target joints. The mean (SD) number of target joints per patient) was 1.4 (0.6), ranging from 1 to 3 target joints per patient.

Efficacy results

Time per Week Spent with the Trough FVIII Level below 1% on the Standard Prophylaxis and after PK-Tailoring

The median time per week spent with the trough FVIII level below 1% was 0.5 hours in patients who were all time on PK-tailored prophylaxis (N=7), the same value in patients who were all time on standard prophylaxis (N=10), and in patients who were shifted from standard to PK-tailored prophylaxis on Visit 2 (N=3).

In the patients who were all time on standard prophylaxis, the 75% percentile (2.4 hours) was higher than in the subgroups of patients who were all time on PK-tailored prophylaxis (75% percentile [0.5 hours]) and patients shifted from standard to PK-tailored prophylaxis on Visit 2 (75% percentile [0.5 hours]). The same trend was observed for the mean value of this parameter, which was 0.5 hours, 6 hours, and 0.5 hours, respectively.

During the study, only 1 (1.06%) patient had more than 19 hours per week spent with a FVIII trough level below 1%. This case was registered in the subgroup of patients who were all time on standard prophylaxis.

Assessor's comment:

Even considering the content of the study protocol, it remains unclear how the time per week spent with a FVIII trough level below 1% (primary endpoint) has been determined, in particular whether it reflects actual measurements (laboratory data records) or merely myPKFit-based predictions. In the case of the latter, and in view of the inclusion criterion *"have individual data of octocog alfa (Advate) half-life ($T_{1/2}$) from myPKFiT application"*, it appears remarkable that (as shown in Table 23 of the clinical study report) the primary endpoint could only be assessed for a small minority of study participants, i.e. 7 of the 35 patients in the "All time on PK-tailored Prophylaxis" group, 10 of the 38 patients in the "All time on standard Prophylaxis" group and 3 of the 21 patients in the "Shifted from standard to PK-tailored" group. The MAH should provide clarification.

Proportion of Patients with Upgraded Dosing Regimen Based on Pharmacokinetic-assessment

An upgrade of dose of octocog alfa based on PK-assessment was required in 5 (5.3%) patients. There were no patients with octocog alfa dosing interval modification.

Assessor's comment:

Despite a total of 56 patients on PK-tailored prophylaxis (35 patients in the "All time on PK-tailored Prophylaxis" group + 21 patients in the "Shifted from standard to PK-tailored" group), Table 26 of the study report reveals only 5 cases of dose modifications. The MAH should further explain this apparent discrepancy.

Proportion of Patients with Time per Week Spent with Factor VIII Trough Level Below 1%, 1-<3%, and ≥3% While on Standard and Individualized Prophylaxis

The endpoint was evaluated only in the subgroup of patients shifted from standard to PK-tailored prophylaxis on Visit 2 (N=19). The subgroup shifted from standard to PK-tailored prophylaxis on Visit 3 was not evaluated due to small size (N=2). At baseline, PK parameters obtained from the last myPKFiT assessment were collected retrospectively or on Visit 1 for all enrolled patients, but the data on PK evaluation after baseline (Visit 1) was available in only 5 patients.

Before changing the regimen (N=19), there were 3 (15.8%), 9 (47.4%), and 7 (36.8%) patients with time per week spent with FVIII trough level below 1%, 1-<3%, and ≥3%, respectively. After changing the regimen (N=5), there were 0 (0.0%), 2 (40.0%), and 3 (60.0%) patients with time per week spent with FVIII trough level below 1%, 1-<3%, and ≥3%, respectively.

Correlation Between the Time Per Week Spent with Factor VIII Trough Level Below 1% (Standard Prophylaxis) or Below 1%, 1-<3%, and ≥3% (PK-tailored Prophylaxis) and Spontaneous Annualized Bleeding Rate and Annualized Joint Bleeding Rate

On standard prophylaxis, the association between the time per week spent with a FVIII trough level below 1% and spontaneous annualized bleeding rate (ABR) was not statistically significant, as shown by Pearson correlation analysis (p=0.479) and Spearman correlation analysis (p=0.378).

On PK-tailored prophylaxis, the association between the time per week spent with a FVIII trough level below 1%, 1-<3%, and ≥3% and spontaneous ABR was not statistically significant, as shown by Pearson correlation analysis (p>0.05 in all cases) and Spearman correlation analysis (p>0.05 in all cases). The association between the time per week spent with FVIII trough level below 1%, 1-<3%, and ≥3% and spontaneous AJBR was also not statistically significant.

Comparisons for Annualized Bleeding Rate and Annualized Joint Bleeding Rate for by Visits and by Shifted Groups

Seventy-five patients with available data on haemorrhages were included in the analysis of this variable.

At Visit 1, comparison of patients on standard prophylaxis versus PK-tailored prophylaxis did not reveal statistically significant differences on ABR (p=0.602, Wilcoxon test) and on AJBR (p=0.919, Wilcoxon test). On standard prophylaxis, the mean (SD) ABR was 1.8 (1.9) and the mean (SD) AJBR was 1.1 (1.3). On PK-tailored prophylaxis, the mean (SD) ABR was 1.6 (2.1) and the mean (SD) AJBR was 0.9 (0.9).

At Visit 2, there were no statistically significant differences between patients on standard prophylaxis versus PK-tailored prophylaxis on ABR (p=0.152, Wilcoxon test) and on AJBR (p=0.321, Wilcoxon test). On standard prophylaxis, the mean (SD) ABR was 0.4 (1.6) and the mean (SD) AJBR was 0.2 (1.3). On PK-tailored prophylaxis, the mean (SD) ABR was 0.9 (2.6) and the mean (SD) AJBR was 0.2 (0.8).

At Visit 3, there were no statistically significant differences between patients on standard prophylaxis versus PK-tailored prophylaxis on ABR (p=0.222, Wilcoxon test) and on AJBR (p=0.676, Wilcoxon test). On standard prophylaxis, the mean (SD) ABR was 0.3 (1.0) and the mean (SD) AJBR was 0.2 (0.7). On PK-tailored prophylaxis, the mean (SD) ABR was 0.7 (1.6) and the mean (SD) AJBR was 0.1 (0.4).

Safety results

Ninety-four male patients were included in the analysis of adverse events (AEs). Forty-seven (50.0%) patients reported a total of 79 AEs, including 5 serious events (SAE) reported in five (5.3%) patients. 74 AEs were assessed as not related to the study treatment, while the relationship of 5 AEs to the study treatment remained unknown. No adverse reactions (i.e. AEs related to the study treatment), deaths, severe AEs, and AEs leading to treatment discontinuation were reported.

Five (5.3%) paediatric patients reported 5 serious adverse events (SAEs), including haemathrosis, haematoma muscle, ingrowing nail, peridonitis, and phimosis, all of which required hospitalization. All SAEs were assessed as not related to the study treatment and were reported as resolved.

2.3.3. Discussion on clinical aspects

In accordance with Article 46 of regulation (EC) No 1901/2006, the MAH submitted the final report of study MACS-2020-051901, together with a short critical expert overview.

Study MACS-2020-051901 (TAK-761-4001; HAPKIDO) was a local, multicenter, non-interventional ambispective study conducted in the Russian Federation in order to identify changes in FVIII trough levels and clinical outcomes in severe haemophilia patients who had been upgraded from standard prophylaxis with octocog alfa (Advate) to myPKFiT-based PK-tailored treatment.

MyPKFiT is an online medical application that allows authorized users to simulate dosing regimens for Advate with patient pharmacokinetic profiles based on only 2 blood samples, which according to the MAH is used in routine clinical practice in approximately 50 Russian clinics.

For study MACS-2020-051901, PK and bleeding data were collected retrospectively (12 months period preceding the first study visit) and / or prospectively (12 months follow-up after enrolment).

The study included a total of 94 male patients, including 83 (88.3%) patients <18 years of age (range: 1–48 years; mean [SD] age: 12.6 [8.2] years). At baseline, 59 (62.8%) patients received standard prophylaxis and 35 (37.2%) patients received individualized PK-tailored prophylaxis. During the course of the study, a total of 21 (22.3%) patients were shifted from standard prophylaxis to PK-tailored treatment.

In essence, results of study MACS-2020-051901 revealed a median time per week spent with a FVIII trough level below 1% of 0.5 hours, irrespective of the underlying prophylaxis regimen (standard vs. PK-tailored). However, a trend towards improved control of FVIII trough levels on PK-tailored prophylaxis vs. standard prophylaxis was seen when comparing the 75% percentiles or mean values of this parameter (2.4 hours vs. 0.5 hours and 6 hours vs. 0.5 hours, respectively).

The proportion of patients with time per week spent with FVIII trough level below 1% was 15.8% (3/19) before regimen changing and 0.0% (0/5) after regimen changing. The proportion of patients with FVIII trough levels ≥3% was 36.8% (7/19) before regimen changing and 60.0% (3/5) after regimen changing.

Neither comparisons of bleeding frequencies (ABRs and AJBRs) between patients on standard prophylaxis and those on PK-tailored prophylaxis, nor correlation analyses of bleeding frequencies and times per week spent below different FVIII trough levels (<1%, 1-<3%, ≥3%) revealed any statistically significant differences or associations.

Safety data obtained during the study indicate a generally well-tolerated treatment and a safety profile consistent with the current labelling without newly identified or additional risks.

However, in addition to the general limitations related to the non-interventional and partly retrospective design of study MACS-2020-051901, interpretation of the reported outcomes is strongly hampered by insufficient information on the underlying methodology (in particular, remaining uncertainties regarding the data sources used to determine weekly times below certain thresholds of plasma FVIII activity) and an overall large proportion of apparently missing data (with, for example, data on the primary endpoint reported for only 20 of the 94 study participants). Furthermore, some of the reported study results raise concerns regarding the credibility of the underlying data sources and should be further discussed by the MAH (as outlined in more detail in section "Request for supplementary information" below).

3. Rapporteur's overall conclusion and recommendation

In summary, the non-interventional data collected in study MACS-2020-051901 do not change the favourable benefit risk profile of Advate in its approved indication. The presented data do not warrant any update of their Product information and no regulatory actions are expected to be required. However, prior to a final recommendation, the MAH should provide some additional information / clarification as outlined in detail in section 4 below.

☒ Not fulfilled:

Based on the data submitted, the MAH should provide additional clarifications on methodological aspects and some of the reported study results as part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

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

1. Even considering the content of the study protocol, it remains unclear how the time per week spent with a FVIII trough level below 1% (primary endpoint) has been determined, in particular whether it reflects actual measurements (laboratory data records) or merely myPKFit-based predictions. In the case of the latter, and in view of the inclusion criterion *"have individual data of octocog alfa (Advate) half-life ($T_{1/2}$) from myPKFiT application"*, it appears remarkable that (as shown in Table 23 of the clinical study report) the primary endpoint could only be assessed for a small minority of study participants, i.e. 7 of the 35 patients in the "All time on PK-tailored Prophylaxis" group, 10 of the 38 patients in the "All time on standard Prophylaxis" group and 3 of the 21 patients in the "Shifted from standard to PK-tailored" group. The MAH should provide clarification.
2. Despite a total of 56 patients on PK-tailored prophylaxis (35 patients in the "All time on PK-tailored Prophylaxis" group + 21 patients in the "Shifted from standard to PK-tailored" group), according to Table 26 of the study report, only 5 patients were affected by dose modifications. The MAH should further explain this apparent discrepancy.
3. The mean (SD) FVIII clearance of 0.0 (0.0) dL/h/kg collected at baseline is considered remarkable and should be further explained / critically discussed.

The timetable is a 30 day response timetable with clock stop.

MAH responses to Request for supplementary information

1. Even considering the content of the study protocol, it remains unclear how the time per week spent with a FVIII trough level below 1% (primary endpoint) has been determined, in particular whether it reflects actual measurements (laboratory data records) or merely myPKFit-based predictions. In the case of the latter, and in view of the inclusion criterion *"have individual data of octocog alfa (Advate) half-life ($T_{1/2}$) from myPKFiT application"*, it appears remarkable that (as shown in Table 23 of the clinical study report) the primary endpoint could only be assessed for a small minority of study participants, i.e. 7 of the 35 patients in the "All time on PK-tailored Prophylaxis" group, 10 of the 38 patients in the "All time on standard Prophylaxis" group and 3 of the 21 patients in the "Shifted from standard to PK-tailored" group. The MAH should provide clarification.

MAH's Response:

The data presented in Table 23 are based on myPKFiT use. Data on the primary endpoint were available for more patients, but many study participants had no decrease of factor VIII (FVIII) below 1%, and patients with a value of 0 for "the time per week spent with a FVIII trough level below 1%" were not included in the calculation of this variable. These data were captured on the electronic case report forms (eCRFs) (in hours) but only patients with non-zero values were included in the analysis (as presented in Section 10.4.1 of the study report). This explains why the total number of patients ("N" in Table 23) is quite small.

Assessment and Conclusion:

The MAH clarified that the calculations summarised in Table 23 of the CSR only included patients with a myPKFiT-based prediction of a certain time per week spent with a FVIII trough level below 1% during prophylaxis.

Issue resolved

2. Despite a total of 56 patients on PK-tailored prophylaxis (35 patients in the "All time on PK-tailored Prophylaxis" group + 21 patients in the "Shifted from standard to PK-tailored" group), according to Table 26 of the study report, only 5 patients were affected by dose modifications. The MAH should further explain this apparent discrepancy.

MAH's Response:

Dose modification was calculated based on the previous dose and the updated dose. Accordingly, only patients with valid data (ie all nonmissing data obtained through routine practice and recorded on the eCRFs) for both doses were included in the calculation of this variable. Taking into account missing data, the analysis of "dose upgrade" included fewer patients than were on PK-tailored prophylaxis. Therefore, 5 patients in Table 26 means that 5 patients had valid data on dose modification and underwent a "dose upgrade".

Assessment and Conclusion:

As clarified by the MAH, only patients with valid data for both, the previous and the updated dose were included in the calculation. Hence, the apparently large proportion of missing data further highlights the only limited informative value of the data obtained in study MACS-2020-051901.

Conclusion: Issue resolved.

3. The mean (SD) FVIII clearance of 0.0 (0.0) dL/h/kg collected at baseline is considered remarkable and should be further explained / critically discussed.

MAH's Response:

The value of clearance was low. These data can be explained by a standard rounding to 1 decimal place. Using rounding to 4 decimal places, the mean (SD) FVIII clearance values can be expressed as 0.0449 (0.0126).

Assessment and Conclusion:

As explained by the MAH, the reported mean (SD) FVIII clearance of 0.0 (0.0) dL/h/kg resulted from rounding of the actual mean (SD) FVIII clearance of 0.0449 (0.0126) dL/h/kg (which falls within the range reflected in section 5.2 of the Advate SmPC) to only one decimal place.

Conclusion: Issue resolved.

5. Rapporteur's overall conclusion and recommendation

☒ Fulfilled:

No regulatory action required.