26 April 2019
EMA/467869/2019
Human Medicines Evaluation Division

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

ELOCTA

efmoroctocog alfa

Procedure no: EMEA/H/C/003964/P46/005.1

Note

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

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1. Introduction

On 18 April 2018, the MAH provided a submission according to Article 46 of the Paediatric Regulation, containing the Clinical Study Report of the Elocta extension study 8HA01EXT (ASPIRE).
A subset of the patient population in the study consists of paediatric subjects. A short expert overview was compiled to meet the requirement of Art. 46 to submit paediatric data within 6 months from End of Study.

In parallel to the Article 46 procedure, an integrated analysis of study 8HA01EXT was ongoing, and filing for a type II Variation for updating clinical data in the SmPC was intended. Results regarding the paediatric population were requested to be consistent with the results presented within the Article 46 procedure, finally.

Two requests for additional information were sufficiently addressed.

2. Scientific discussion

2.1. Information on the development program

Study 8HA01EXT was a phase 3, open-label, multicenter, extension study comprising 240 previously treated male subjects with hemophilia A (congenital factor VIII [FVIII] deficiency). The objectives of the study were to evaluate the long-term safety and efficacy of recombinant factor VIII Fc fusion protein (rFVIIIFc) in the prevention and treatment of bleeding episodes, as routine prophylaxis, and for perioperative management. The study was conducted in accordance with Good Clinical Practice.

The subjects had completed a preceding study of rFVIIIFc, including study 8HA02PED (Kids- A-LONG; subjects <12 years of age), study 997HA301 (A-LONG; subjects ≥12 years of age), study 997HA307 (subjects ≥12 years of age) or study 997HA309 (subjects ≥12 years of age). Participation in 8HA01EXT would allow subjects in the above studies to remain on treatment with rFVIIIFc until commercially available. The study was terminated in October 2017.

The extension study data alone does not lead to regulatory consequences before an integrated analysis with the parent studies has been finalized. This integrated analysis is ongoing, and results thereof will be submitted as a Type II variation, together with updates to the Product Information and Risk Management Plan, during Q3 2018.

2.2. Clinical aspects

2.2.1. Introduction

rFVIIIFc is a protein consisting of B-domain deleted coagulation FVIII covalently attached to the Fc domain of human immunoglobulin G1 to achieve reduced clearance and thus an extended half-life in plasma. rFVIIIFc replaces the missing endogenous FVIII needed for effective hemostasis in subjects with hemophilia A.

Compared to conventional FVIII products, rFVIIIFc reduces the number of intravenous injections, which ease the burden of treatment and may improve the quality of life and treatment adherence.

rFVIIIFc also offers the opportunity for reduced time below critical FVIII activity levels at which there may be an increased risk of bleeding events (Collins et al. 2009).

rFVIIIFc was approved in the EU on November 19, 2015, for the treatment and prophylaxis of bleeding in subjects with hemophilia A. The product is also approved in e.g., the US, Canada, Japan, Australia, and Switzerland.

The original marketing authorization application for rFVIIIFc was based on 1 phase 1/2a dose escalation study (998HA101) and 2 pivotal phase 3 studies (8HA02PED and 997HA301).

2.2.2. Clinical study 8HA01EXT (MAH Expert Overview)

Study population and treatment regimens

A total of 240 male subjects exposed to rFVIIIFc were included in the safety and efficacy evaluation, of which 61 subjects were enrolled from study 8HA02PED (30 subjects <6 years of age; 31 subjects 6 to <12 years of age), and 179 subjects were enrolled from studies 997HA301 (150 subjects), 997HA307 (13 subjects) and 997HA309 (16 subjects) combined.

The total subject-years followed on the study were 730.30 years (excluding major surgical periods). The exposure to rFVIIIFc was up to 203.0 weeks (mean 143.22 weeks) in study 8HA02PED, and up to 274.6 weeks (mean 162.45 weeks) in studies 997HA301, 997HA307 and 997HA309 combined. Retention was high, as was subject treatment adherence. These data allowed for robust long-term safety and efficacy evaluations.

Treatment regimens differed depending on age group, with subjects <12 years of age receiving either tailored prophylaxis or personalized prophylaxis, and subjects ≥12 years of age receiving either tailored prophylaxis, personalized prophylaxis, weekly prophylaxis, or episodic regimen, with the opportunity to change regimen during the study to enable optimization of dosing schedule to achieve protection from bleeding and/or lessening of treatment burden.

Tailored prophylaxis: Doses of 25 to 65 IU/kg rFVIIIFc every 3 to 5 days, or dosing 2 times per week at approximately 20 to 65 IU/kg rFVIIIFc on Day 1 and 40 to 65 IU/kg rFVIIIFc on Day 4. In subjects <12 years of age, dose adjustments up to a maximum prophylactic dose of 80 IU/kg and frequency of administration up to every 2 days was used if necessary to maintain adequate FVIII activity trough levels and prevent spontaneous bleeding events.

Weekly prophylaxis: Once weekly dosing of approximately 65 IU/kg.

Personalized prophylaxis: If optimal prophylaxis dosing could not be achieved using either tailored or weekly prophylaxis, the investigator further personalized the dose to meet the needs of individual subjects.

Episodic regimen: The individual dose of rFVIIIFc to treat bleeding episodes was based on the subject's clinical condition and the type and severity of the bleeding event.

Summary of clinical data

Safety results

General statement regarding the pediatric population

No unique safety issues were observed in subjects <12 years of age, and the type of adverse events (AEs) observed were generally similar to what is expected for the pediatric hemophilia population.

Primary analysis

The primary objective of study 8HA01EXT was to evaluate the long-term safety of rFVIIIFc, with the primary endpoint being the occurrence of inhibitor development. Additional exposure to rFVIIIFc in study 8HA01EXT contributed further to the assessment of inhibitor development.

No subjects developed an inhibitor to FVIII during the study.

Long-term safety evaluation

The type and incidence of AEs observed were generally similar to what is expected for the general pediatric and adult hemophilia population. There were 3 treatment-emergent AEs in 2 subjects (enrolled from study 997HA301) assessed as related to rFVIIIFc treatment, of which 1 subject experienced headache and hot flush, and 1 subject experienced chromaturia.

219 subjects were evaluated with regards to anti-rFVIIIFc antibodies, of which 217 subjects were negative throughout the study, and all subjects were negative at the final evaluation. Assessment of anti-rFVIIIFc antibodies remains exploratory, and the clinical significance is unknown.

There were no reports of anaphylaxis or serious hypersensitivity events associated with rFVIIIFc.

No patterns or trends were observed in abnormalities of hematology, clinical chemistry, or vital signs.

No deaths occurred during the study.

Efficacy results

General statement regarding the pediatric population

The efficacy of rFVIIIFc treatment in the prevention and treatment of bleeding episodes in the pediatric population was similar to that in the adult population. The annual drug consumption was highest for the age group 0 to 6 years, and the age group 6 to 12 years had higher annual drug consumption than adults and adolescents. This is in line with the results from the pivotal studies on rFVIIIFc and reflects the faster elimination of rFVIIIFc (and other FVIII replacement products) in younger subjects.

Long-term efficacy evaluation

The secondary objective of study 8HA01EXT was to evaluate the efficacy of rFVIIIFc in the prevention and treatment of bleeding episodes.

rFVIIIFc was highly effective as prophylaxis and in the treatment of bleeding episodes in both pediatric and adult subjects. The annualized bleeding rates were low in prophylactic treated cohorts in both pediatric and adult subjects, and the annualized bleeding rates were consistently lower in the prophylactic regimens as compared to the episodic regimen in adolescent and adult subjects.

The physician’s global assessment of the subjects' responses to their rFVIIIFc regimen was considered mostly excellent and effective at the subjects’ visits, and no response was assessed as ineffective at any visit.

The efficacy of rFVIIIFc in controlling the bleeding episodes was maintained over time. The majority of rFVIIIFc first injections were rated by the subject as producing excellent or good responses. In addition, more than 93 % of subjects in each treatment arm were controlled with ≤2 rFVIIIFc injections, with more than 75 % of subjects being controlled by only 1 injection.

rFVIIIFc was highly effective in the perioperative management. Hemostasis during major surgery was rated as excellent or good, indicating that intraoperative blood loss was comparable to what would be expected for a subject who did not have hemophilia A.

Most subjects received high scores on the quality of life assessments at baseline, indicating that the self-perceptions of health-related and non-health-related aspects of well-being were high.

These results were maintained throughout the study.

The ongoing integrated analysis with the respective parent studies will give further insights into long-term treatment with rFVIIIFc.

2.2.3. Discussion on clinical aspects (Assessor)

Submitted Short Critical Expert Overview briefly reflects a summary of extension study 8HA01EXT ASPIRE. Furthermore, a high-level general statement regarding safety and efficacy in the paediatric population is provided.

However, an evaluation of paediatric data supporting the general statement on safety and efficacy is missing. Summaries of clinical data cover the whole study population (children and adults), and reflect vague information besides the patient numbers (61 pts out of 240; 30 < 6 years and 31 6-12 years), only.

Evaluation should cover the complete paediatric population (0-18 years of age) and address all paediatric sub-populations (0-6, 6-12, above 12 years of age). Furthermore, grounds and analysis supporting the general statement on safety and efficacy should be presented within the overview. Key efficacy- and safety-results for respective sub-populations (in comparison to adults' data) should be available, covering e.g. the different treatment regimens, factor consumption per kg and year, and safety profile for each age-group.

The MAH stated that an integrated analysis of study 8HA01EXT is currently ongoing. Results regarding the paediatric population should be consistent with the results presented within the Article 46 procedure.

3. CHMP's overall conclusion and recommendation

The MAH submitted a Short Critical Expert Overview which briefly reflected a brief summary of extension study 8HA01EXT ASPIRE and a high-level general statement regarding safety and efficacy in the paediatric population.

However, the overview was not considered to be comprehensive for reflecting the paediatric data from the respective study as the presented analysis was vague and incomplete.

The MAH stated that an integrated analysis of study 8HA01EXT was currently ongoing. Results regarding the paediatric population were requested to be consistent with the results presented within the Article 46 procedure.

Based on the data submitted, the MAH should provide additional clarifications. (see section 4 "Additional clarification requested")

4. Additional clarification requested

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

(1) Concise results of the evaluation of paediatric data supporting the general statement on safety and efficacy are requested. These should cover the complete paediatric population (0-18 years of age) and address all paediatric sub-populations (0-6, 6-12, above 12 years of age). Furthermore, grounds and analysis supporting the general statement on safety and efficacy should be presented: Key efficacy- and safety-results for respective sub-populations (in comparison to adults' data) should be available, covering e.g. the different treatment regimens, factor consumption per kg and year, and safety profile for each age-group, respectively.

(2) The MAH stated that an integrated analysis of study 8HA01EXT is currently ongoing. Results regarding the paediatric population should be consistent with the results presented within the Article 46 procedure. The MAH is asked to confirm and provide respective evaluation within the proposed variation, as well.

(3) The MAH is asked to provide a Line listing of all the studies included in the development program as outlined in the Annex.

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

5. MAH responses to Request for supplementary information

Question 1

Concise results of the evaluation of paediatric data supporting the general statement on safety and efficacy are requested. These should cover the complete paediatric population (0-18 years of age) and address all paediatric sub-populations (0-6, 6-12, above 12 years of age). Furthermore, grounds and analysis supporting the general statement on safety and efficacy should be presented: Key efficacy- and safety-results for respective sub-populations (in comparison to adults' data) should be available, covering e.g. the different treatment regimens, factor consumption per kg and year, and safety profile for each age-group, respectively.

MAH's responses

The clinical development program for Elocta was designed in accordance with the "Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products" (EMA/CHMP/BPWP/144533/2009). This guideline stipulates pre-authorisation studies on a) minimum 50 previously treated patients ≥12 years of age for 50 exposure days and b) a paediatric study on minimum 25 previously treated patients in the age group 6-12 years for 50 exposure days and minimum 25 patients <6 years of age for 50 exposure days. The guideline does not define the age group 12-18 years as a specific goup, they are considered included in the adult study population. The study designed to meet requirements a) in the clinical development program for Elocta was study 997HA301 (A-LONG) and corresponding study for requirement b) was study 8HA02PED (Kids A-LONG).

Following the two pre-authorisation studies, the guidelines stipulates a post-authorisation study on 200 previously treated patients (including the patients from the pre-authorisation study) for a total of 100 exposure days, whereof at least 60 patients ≤ 12 years of age. The study designed to meet this requirement on a post-authorisation study was the extension study 8HA01EXT (ASPIRE) that is being reported in this Article 46 submission. The agreed paediatric investigation plan for Elocta (EMEA-001114-PIP01-10) refers to study 8HA01EXT without further specifying requirements on paediatric age groups in the study population. As a result, 8HA01EXT study data for age groups 0-6 and 6-12 can be fully extracted, whereas specific data for the age group 12-18 is limited to safety data.

In study 8HA01EXT, a total of 240 male subjects exposed to rFVIIIFc were included in the safety and efficacy evaluation, of which 61 subjects were enrolled from study 8HA02PED (30 subjects <6 years of age; 31 subjects 6 to <12 years of age), and 179 subjects were enrolled from studies 997HA301 (150 subjects), 997HA307 (13 subjects) and 997HA309 (16 subjects)

combined. All subjects enrolled into 8HA01EXT were already on treatment with Elocta, and baseline data were not collected at the start of ASPIRE but only at start of the parent study. 23 subjects that belonged to the age group 12-18 years at start of study 997HA301, 997HA307 or 997HA309 were enrolled into the extension study 8HA01EXT (Ref. Table 16 in Module 2.7.4 Summary of Clinical Safety submitted to EMA on July 16, 2018 in the Type II variation EMEA/H/C/003964/II/0026 that is currently under assessment).

Key efficacy results from study 8HA01EXT for the age groups 0-6, 6-12 and >12 years are presented in the tables on the two following pages (extracted from Module 2.7.3 Summary of Clinical Efficacy submitted to EMA on July 16, 2018 in the Type II variation EMEA/H/C/003964/II/0026 that is currently under assessment).

It can be seen that the annualized bleeding rate is low and similar for all age groups on prophylactic treatment regimens and has remained at the same levels from the parent studies into the extension study. As expected, factor consumption (IU/kg) was highest for the age group 0 to 6 years, and the age group 6 to 12 years had a higher drug consumption (IU/kg) than adults and adolescents. This is in line with the results from the pivotal studies on rFVIIIFc and reflects the faster elimination of rFVIIIFc (and other FVIII replacement products) in younger subjects.

0-6 years:	5722.0
6-12 years:	5203.6
>12 years:	4866.5

Annualized factor consumption (IU/kg) for the different age cohorts on individualized prophylaxis in study 8HA01EXT were as follows: (Ref: Study 8HA01EXT CSR Table 63, Table 64, Table 65)

Assessment of the MAH's responses

Study-design of the pivotal and extension studies followed the requirements of the Clinical Guideline.

Evaluation within the Article 46 procedure has its focus on the paediatric age group and potential implications for the SmPC. Requested key efficacy-parameters include annual consumption, the Physician's assessment of treatment response for major bleeding episodes, and it might include the annual bleed rate although not standardized and not comparable between different study-protocols.

Annual consumption-data have been amended. However, the consumption of 4866.5 IU/kg/year for >12 year old subjects covers the complete adult population and not the paediatric sub-group below 18 years. According to ICH E11 and the Paediatric Regulation respective patient-group is a paediatric sub-group and therefore target of the article 46 procedure. Amendment of such data is requested (Q)

Key efficacy endpoints have been amended for the paediatric age-groups below 12 years. However, similar to the consumption-data, the age-group 12-18 years should be amended (Q)

Safety-outcome has been presented within the Response with reference to respective Table 26 from Variation II/26. Conclusion is considered to be adequate.

Conclusion

Valuable evaluation has been amended based upon the data from Variation II/26. However, key efficacy endpoints including annual consumption of the factor concentrate (IU/kg/year) should be amended for the age-group of 12-18 years, accordingly (Q).

Question 2

The MAH stated that an integrated analysis of study 8HA01EXT is currently ongoing. Results regarding the paediatric population should be consistent with the results presented within the Article 46 procedure. The MAH is asked to confirm and provide respective evaluation within the proposed variation, as well.

MAH's responses

The integrated analysis of study 8HA01EXT with its parent studies was submitted to EMA on July 16, 2018 in the Type II variation EMEA/H/C/003964/II/0026 and is currently under assessment. It presents data on treatment with Elocta in paediatric subject over a median of 178.0 (range 2.0, 229.4) cumulative weeks. The data supporting the responses to Question 1 are drawn from this integrated analysis. The MAH confirms that results are consistent between the variation and the Article 46 procedure. What the integrated data shows in addition is the beneficial effect of long-term treatment with Elocta on joint health status, when evaluating the subjects joint health status at the baseline of the respective parent studies 997HA301 (>12 years of age) and 8HA02PED (≤12 years of age). The integrated evaluation that is referred in these responses and submitted in variation EMEA/H/C/003964/II/0026 is found here:

Module 2.5 Clinical Overview (ASPIRE integrated)

Module 2.7.3 Summary of Clinical Efficacy (ASPIRE integrated)

Module 2.7.4 Summary of Clinical Safety (ASPIRE integrated)

Assessment of the MAH's responses

The Article 46 procedure and a subsequently submitted variation procedure II/26 regarding updating Section 5.1 of the SmPC share the same data-base-extension (study 8HA01EXT). Unfortunately, the evaluation of paediatric data has only been presented within the second procedure – resulting in some confusion and shortages for the article 46 procedure.

However, the MAH confirms consistency of the results of the variation and the Article 46 procedure. Requested updates from the variation procedure need to be incorporated in the documentation, herein.

Conclusion

Point solved

Question 3

The MAH is asked to provide a Line listing of all the studies included in the development program as outlined in the Annex.

MAH's responses

The requested Line Listings were provided with the initial Article 46 submission (annex to cover letter).

Assessment and Conclusion

Point solved

6. CHMP's overall conclusion and recommendation according to the assessment of the responses to RSI

The Article 46 procedure and a subsequently submitted variation procedure II/26 regarding updating Section 5.1 of the SmPC share the same data-base-extension (study 8HA01EXT). Unfortunately, the evaluation of paediatric data had only been presented within the second procedure – resulting in some confusion and shortages for the article 46 procedure. Requested updates from the variation procedure needed to be incorporated in the documentation, herein.

However, the MAH confirmed consistency of the results of the variation and the Article 46 procedure.

Evaluation within the Article 46 procedure has its focus on the paediatric age group. Requested key efficacy-parameters include annual consumption, the Physician's assessment of treatment response for major bleeding episodes, and it might include the annual bleed rate although not standardized and not comparable between different study-protocols.

Annual consumption-data and key efficacy-data had been amended for the paediatric age-groups <12 years. However, respective data for the paediatric subgroup 12-18 years should be amended, in addition.

Safety-outcome has been presented within the Response with reference to respective Table 26 from Variation II/26.

Based on the data submitted, the MAH should provide additional clarifications. (see section 7 "Additional clarification requested")

7. List of Outstanding Issues

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

(1) Annual consumption-data and key efficacy-data have been provided for the paediatric age-groups <12 years. However, respective data for the paediatric subgroup 12-18 years should be amended.

(2) Consistency of herein presented data and requested updates from the variation procedure (II/26) should be ensured.

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

8. MAH responses to 2nd Request for supplementary information

Question 1

Annual consumption-data and key efficacy-data have been provided for the paediatric age-groups <12 years. However, respective data for the paediatric subgroup 12-18 years should be amended.

Summary of MAH's response

A post-hoc analysis was done on the data from studies 997HA301 and 8HA01EXT. Fourteen adolescent patients in the age group 12-17 years were identified at the start of the extension study 8HA01EXT. Two had on-demand treatment throughout both studies, so eleven subjects were evaluable for efficacy of prophylactic treatment in study 997HA301 and twelve in study 8HA01EXT.

Median annual factor consumption was 5572 IU/kg (min 3849, max 7035) in Study I and 4456 IU/kg (min 3563, max 8011) in Study III. Respective median ABR was 1.92 (min 0, max 7.1) and 1.25 (min 0, max 9.5).

The following text was included in the SmPC section 5.1:

12 adolescent subjects age 12 up to 18 years were included in the adult study population on prophylactic treatment. Median annual factor consumption was 5572 IU/kg (min 3849, max 7035) in Study I and 4456 IU/kg (min 3563, max 8011) in Study III. Respective median ABR was 1.92 (min 0, max 7.1) and 1.25 (min 0, max 9.5).

Assessment and Conclusion

Requested parameters have been evaluated and reflected within section 5.1 of the SmPC.

Issue resolved.

Question 2

Consistency of herein presented data and requested updates from the variation procedure (II/26) should be ensured.

MAH's responses

The MAH confirms that the key efficacy data for adolescents provided in response to Question 1 are identical to the data provided in variation0026 (EMEA/H/C/003964/II/0026).

Assessment and Conclusion

Issue resolved.

9. CHMP's overall conclusion and recommendation according to the assessment of the responses to 2nd RSI

☒ **PAM fulfilled**