Taiwan Food and Drug Administration

Assessment Report

Trade Name： **奧妥凝凍晶注射劑 250 國際單位/ALTUVIIIO Lyophilized powder for solution for intravenous injection 250 IU**
奧妥凝凍晶注射劑 500 國際單位/ALTUVIIIO Lyophilized powder for solution for intravenous injection 500 IU
奧妥凝凍晶注射劑 1000 國際單位/ALTUVIIIO Lyophilized powder for solution for intravenous injection 1000 IU
奧妥凝凍晶注射劑 2000 國際單位/ALTUVIIIO Lyophilized powder for solution for intravenous injection 2000 IU

Active Ingredient：Efanesoctocog alfa (BIVV001)

License Number：MOHW-BI 001234
MOHW-BI 001235
MOHW-BI 001236
MOHW-BI 001237

Applicant：賽諾菲股份有限公司

Approval Date：2023/7/13

Indication：
適用於 A 型血友病(先天性第八凝血因子缺乏症)病人，可用於：常規預防以減少出血頻率、需要時治療及控制出血事件、手術療程處置。
使用限制: 本品不適用於治療溫韋伯氏病(von Willebrand disease)。

ALTUVIIIO, is indicated in patients with hemophilia A (congenital factor VIII deficiency) for:

- **Routine prophylaxis to reduce the frequency of bleeding episodes,**
- **On demand treatment and control of bleeding episodes,**
- **Perioperative management of bleeding.**

Limitation of Use

ALTUVIIIO is not indicated for the treatment of von Willebrand disease.

Background Information

Trade Name	奧妥凝凍晶注射劑 250 國際單位 /ALTUVIIIO Lyophilized powder for solution for intravenous injection 250 IU 奧妥凝凍晶注射劑 500 國際單位 /ALTUVIIIO Lyophilized powder for solution for intravenous injection 500 IU 奧妥凝凍晶注射劑 1000 國際單位 /ALTUVIIIO Lyophilized powder for solution for intravenous injection 1000 IU 奧妥凝凍晶注射劑 2000 國際單位 /ALTUVIIIO Lyophilized powder for solution for intravenous injection 2000 IU
Active Ingredient(s)	Efanesoctocog alfa(BIVV001)
Applicant	賽諾菲股份有限公司
Dosage Form & Strengths	凍晶注射劑
Indication	適用於 A 型血友病(先天性第八凝血因子缺乏症)病人，可用於：常規預防以減少出血頻率、需要時治療及控制出血事件、手術療程處置。 使用限制: 本品不適用於治療溫韋伯氏病 (von Willebrand disease)。 ALTUVIIIO is indicated in patients with hemophilia A (congenital factor VIII deficiency) for: ● Routine prophylaxis to reduce the frequency of bleeding episodes, ● On demand treatment and control of bleeding episodes, ● Perioperative management of bleeding. Limitation of Use ALTUVIIIO is not indicated for the treatment of von Willebrand disease.
Posology	詳如仿單
Pharmacological Category ATC Code	B02BD06

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance (DS)

General information

Efanesoctocog alfa is a fully recombinant fusion protein comprising a single chain B-domain deleted (BDD) analogue of human FVIII covalently fused to the Fc domain of human immunoglobulin G1 (IgG1), the FVIII-binding D'D3 domain of human von Willebrand factor (VWF), and 2 XTEN polypeptides. The Fc, VWF, and XTEN portions of the molecule extend the half-life of Efanesoctocog alfa in plasma.

Manufacture

Efanesoctocog alfa is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line. The efanesoctocog alfa manufacturing process is described including the material inputs, critical process parameters, and process outputs (in-process controls, microbial controls, and performance attributes) and supported process robustness, as demonstrated during process validation. Efanesoctocog alfa is manufactured without addition of human- or animal-derived components. The raw materials used during the production of Efanesoctocog alfa are either of compendial quality or are tested according to in-house specifications to ensure their quality. There is one DS process change in the manufacturing process history. To evaluate comparability of manufacturing process change, comparability studies were performed such as lot release tests, process-related impurity, characterization tests, and stability. The comparability results demonstrated the process changes still maintain DS quality.

Characterization

Characterization tests are physicochemical and biological properties of the product, including primary structure, higher order structure, carbohydrate structure, charge and size heterogeneity, and biological properties. Process-related impurities and product-related impurities were within the specification for release and stability tests.

Control of DS

The specification of DS was provided and the acceptance criteria is well-justified. All batch results were within acceptable criteria to demonstrate DS quality consistency. In addition, Certification of Analysis (CoA) shows that analytical results meet specification requirements.

Stability

The proposed self-life is 60 months at -60 °C to -90 °C (long-term storage condition). The long-term stability test is still ongoing, including, three commercial process performance qualifications batches. The current stability results support the DS is stable at -60 °C to -90

°C for 60 months.

2.1.2 Drug product (DP)

Description of DP

The DP is a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution for intravenous injection. The product is supplied in single-dose vials containing nominal potencies of 250, 500, 1000, or 2000 international units (IU). The final DP contains the excipients: sucrose (5% w/v), calcium chloride dihydrate (5 mM), histidine (10 mM), arginine hydrochloride (250 mM) and polysorbate 80 (0.05% w/v). Each vial of DP is labeled with the actual content in IU. The powder for injection is reconstituted with 3 mL sterile water for injection (sWFI) supplied in a sterile prefilled syringe through a sterile vial adapter reconstitution device.

Pharmaceutical Development

There is one process change during manufacturing process development. Comparability studies contain lot release test, characterization test, stability test. All results were within acceptance criteria. The compatibility and safety of the container closure system are demonstrated by stability study, extractable and leachable study. The manufacturers and batch formula of DP are presented. The process controls and parameters are presented in manufacturing process description. The process validation results meet the acceptance criteria to support process consistent quality.

Control of DP

The specification of DP is provided and the acceptance criteria is well-justified. Release results and CoAs are within acceptance criteria.

Stability

The results of accelerated stability and long-term stability data are provided and supported 48 months of shelf-life for DP stored at 5 ±3 °C and short-term sequential room temperature up to 30 °C storage for up to 6 months.

Overall, the quality results include the manufacturing process, control of materials, in-process controls, characterization, specifications, container closure system, and stability. These results adequately support that the manufacturing of DP is well-controlled and quality consistency.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Efanesoctocog alfa is a novel recombinant fusion protein for the factor VIII (FVIII)

replacement therapy. The activity of the intrinsic and common pathways of coagulation, the ability of FVIII to act as a cofactor for FIXa activation of FX, effects on the clotting time and thrombin generation potential, and kinetics of fibrin fiber formation and thrombin activation were demonstrated in a series of in vitro assays for efanesoctocog alfa. The in vivo efficacy of efanesoctocog alfa on coagulation was shown in the tail clip bleeding model and tail vein transection model using FVIII deficient mice. Safety endpoints regarding cardiovascular (monkey), respiratory (rat) or central nervous system (rat) functions were evaluated in 4-week repeated-dose toxicity studies; no adverse changes were noted up to the highest dose examined.

2.2.2 Toxicological Studies

In 4-week repeated-dose toxicity studies, no adverse changes were noted up to the highest dose examined in rats or monkeys. One male monkey of the recovery group died due to blood loss secondary to venipuncture and impaired hemostasis, consistent with the development of neutralizing antibodies against endogenous FVIII. Anti-drug antibodies (ADAs) were detected in efanesoctocog alfa-treated rats and monkeys. In accordance with the ICH S6(R1) guidance, it is acceptable that no standard genotoxicity studies are conducted with efanesoctocog alfa. A comprehensive assessment supported that efanesoctocog alfa has little or no carcinogenic potential.

Considering the product property, known mechanism of action, results of completed toxicity studies, potential ADA formation in animals, physiological alterations in pregnant animals, and target patient population, it is acceptable that no reproductive toxicity studies are conducted with efanesoctocog alfa. An in vitro hemocompatibility study with human whole blood showed no hemolysis or plasma flocculation for efanesoctocog alfa treatment.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Efanesoctocog alfa is a long-acting recombinant fusion protein developed for the treatment of hemophilia A in adult and children. The dose of Efanesoctocog alfa for routine prophylaxis is 50 IU/kg once weekly via intravenous injection. It was designed to have longer half-life compared to other approved FVIII products. The mean terminal plasma half-life of efanesoctocog alfa was about 3.8- and 2.7-fold times the half-life of Advate® and Adynovi® (Adynovate®), respectively.

Dose proportionality was observed for C_{max} and AUC with doses ranging from 25 IU/kg to 65 IU/kg. Weekly dosing of 50 IU/kg of efanesoctocog alfa showed minimal accumulation. With once weekly dose at 50 IU/kg, efanesoctocog alfa can provide FVIII activity in the normal to near-normal range (> 40 IU/dL) for 3 to 4 days in adults and adolescents and for 2 to 3 days in children <12 years of age. At the end of the weekly dosing interval, FVIII activity can still

maintain >10 IU/d or above the mild hemophilia range (>5 IU/dL) in all age groups. Higher clearance was observed in pediatric subjects. Thus, the exposure of BIVV001 at steady state in pediatrics younger < 12 years of age was lower than that observed in adults and adolescents administered 50 IU/kg once weekly dose.

Based on population PK analysis, the volume of distribution of efanesoctocog alfa was 38.6 mL/kg. Efanesoctocog alfa is a protein and hence metabolized by degradation into small peptides and individual amino acids. The clearance of efanesoctocog alfa was 0.553 mL/h/kg, and half-life was 48.4 hours, in a typical patient with body weight of 78.3 kg.

In treatment period of clinical trials, no subjects developed neutralizing antibodies (inhibitor) to FVIII. Besides, the incidence of treatment-emergent anti-drug antibodies (ADAs) was low (2.2%), and the ADA response was transient. The presence of treatment-emergent ADA did not appear to have an effect on the PK of efanesoctocog alfa.

2.3.2 Interaction Studies

No drug-drug interaction was conducted.

2.3.3 Special Populations

The population PK analysis showed that body weight was a statistically significant covariate on both clearance (CL) and volume of distribution (V). Younger children with lower body weight had higher clearance and lower exposure at steady state compared to adults and adolescents. Age, VWF antigen levels, hematocrit, blood type, and HCV/HIV status had no impact on BIVV001 PK profiles.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The pivotal Phase 3 study (EFC16293) in adult and adolescent previously treated patients (PTPs) ≥ 12 years of age with severe hemophilia A was reviewed to evaluate the efficacy of efanesoctocog alfa (also known as BIVV001).

Participants on a pre-study prophylaxis treatment were enrolled in Arm A (N=133) for prophylaxis treatment with BIVV001 50 IU/kg once weekly for 52 weeks, and participants on a pre-study on-demand treatment regimen were enrolled in Arm B (N=26) for on-demand treatment for 26 weeks with BIVV001 50 IU/kg and thereafter switched to prophylaxis with BIVV001 50 IU/kg once weekly for 26 weeks. The majority of participants enrolled in Arm A had previously completed Study OBS16221 (an observational study of patients receiving a marketed FVIII replacement therapy for up to 12 months).

Following the analysis of the primary efficacy endpoint (annualized bleeding rate [ABR] in Arm A), the key secondary endpoints (i.e., intra-participant comparison of BIVV001 weekly prophylaxis treatment versus pre-study FVIII prophylaxis [non-inferiority followed by superiority]), and the 3 selected secondary endpoints (Haem-A-QoL Physical Health, PROMIS Pain intensity 3a [past 7 days intensity of pain at its worst score], and Hemophilia Joint Health Score [HJHS] total score) were analyzed as part of a hierarchical testing procedure.

The study met the primary endpoint, ABR in Arm A: The estimated mean ABR was 0.71 (95% CI: 0.52, 0.97). The upper limit of the 1-sided 97.5% CI was substantially less than the prespecified value of 6, demonstrating that the weekly prophylaxis treatment regimen with BIVV001 provided effective protection against bleeds.

The study met the key secondary endpoints: Intra-participant comparison demonstrated the non-inferiority of BIVV001 prophylaxis as the upper bound of the 1-sided 97.5% CI of the estimated mean difference between BIVV001 prophylaxis and pre-study prophylaxis (difference: -2.30; 95% CI: -3.49, -1.11) was below the prespecified NI margin of 4 bleeds per year. Superiority of BIVV001 prophylaxis as compared with pre-study prophylaxis was also demonstrated with a rate ratio of 0.23 (95% CI: 0.13, 0.42) and p-value <0.0001, showing a reduction of 77% in estimated mean ABR.

The study met the selected secondary endpoints: The estimated mean change from baseline to Week 52 in Haem-A-QoL Physical Health score (aged 17 years or above; n=98), PROMIS Pain Intensity first item score and HJHS Total score were -6.74 (95% CI: -10.13, -3.36; p-value=0.0001), -0.21 (95% CI: -0.41, -0.02; p-value=0.0276), and -1.54 (95% CI: -2.70, -0.37; p=0.0101), respectively, demonstrating a statistically significant improvement.

For 26 participants in Arm B, the estimated mean ABR was 21.41 (95% CI: 18.81, 24.36) with on-demand treatment and 0.70 (95% CI: 0.33, 1.48) when participants switched to prophylaxis treatment. The estimated mean ABR with prophylaxis treatment was similar to the one observed in Arm A.

Study EFC16295 was a Phase 3, open-label, single-arm study in previously treated pediatric patients < 12 years of age with severe hemophilia A. A total of 74 participants were enrolled and treated with BIVV001 50 IU/kg once weekly for 52 weeks. The primary endpoint was the occurrence of inhibitor, and the efficacy endpoints were analyzed descriptively. The routine prophylaxis resulted in a mean ABR of 0.48 (95% CI: 0.30, 0.77) and 1.33 (95% CI: 0.64, 2.76) in children < 6 years and 6 to 12 years of age, respectively.

In Study EFC16293, a total of 362 bleeding episodes were treated with BIVV001, mostly occurring on Arm B subjects during the on-demand period. The majority (96.7%) of bleeding episodes were resolved after a single injection of 50 IU/kg. In Study EFC16295, a total of 64 bleeding episodes were treated with BIVV001. Bleeding was resolved with a single 50 IU/kg injection of BIVV001 in 81.3% of bleeding episodes. The median (Q1; Q3) total dose to treat a bleeding episode was 52.6 IU/kg (51.6; 61.0). While excluding one subject who did not receive the regular prophylaxis as specified in the protocol, 41 of the 43 bleeding episodes (95.3%) were resolved with a single 50 IU/kg injection.

Perioperative management was assessed in 21 major surgeries and 22 minor surgeries in adults and pediatric patients. Most of the surgeries required a single pre- operative dose of 50 IU/kg to maintain hemostasis, and none of the participants required blood component transfusion during the surgical period. The hemostatic effect of BIVV001 was rated as "excellent" by all the investigators or surgeons.

2.4.2 Safety Results

The safety data were mainly pooled from 159 subjects of Study EFC16293 (mean exposure day [ED] 48.4) and 74 subjects of Study EFC16295 (mean ED 52.5). The most common AEs were headache, arthralgia, fall, and back pain in adults and adolescents, and the most common AEs in children were positive SARS-CoV-2 tests, upper respiratory tract infection, and pyrexia. 9.4% of the participants in Study EFC16293 and 12.2% of the participants in Study EFC16295 experienced SAEs, and none of these events were assessed as related to efanesoctocog alfa.

No neutralizing antibodies (inhibitors) to FVIII was detected in all the previously treated patients (PTP) during clinical trials. Four participants in Study EFC16293 Arm B developed transient treatment-emergent ADA, and no specific TEAE pattern was observed for these subjects. Three thromboembolic events occurred in Study LTS16294, but all of the subjects had pre-existing risk factors.

Overall, efanesoctocog alfa was well tolerated with no unexpected safety issues compared to other approved FVIII products. In view of the limited number of patients in the pre-authorization trials, further safety information from long-term follow-up Study LTS16294 should be submitted for review once completed.

2.5 Bridging Study Evaluation

Based on the study result, the East Asian participants had higher exposure (AUC: ↑ 9.4%), lower clearance (↓10.6%) and longer half-life than the overall population. Pop-PK analysis also showed that Asian patients had higher FVIII activity exposures than those in Non-Asian

patients in each age group. However, the PK differences between Asian and non-Asian population was not considered clinically meaningful. No dose adjustment was required based on race (East Asian).

There were 21 (13.2%) East Asian participants enrolled from Taiwan, Japan, and Korea in Study EFC16293. Overall, the efficacy results of efanesoctocog alfa for prophylaxis, treating bleeding episodes, and perioperative management were similar between East Asian and the overall population. Additional safety data was collected from 7 Taiwanese participants in Study EFC16295, 15 participants rolled over from EFC16293 to LTS16294 Arm A, and 32 Chinese participants in LTS16294 Arm B. The safety profile of East Asian subjects was consistent with that of the overall population. The ethnic difference of clinical efficacy and safety was minimal, thus the bridging study could be waived.

2.6 Conclusion

In conclusion, efanesoctocog alfa as the routine prophylaxis to reduce the frequency of bleeding episodes, on demand treatment and control of bleeding episodes, and perioperative management of bleeding in adults and pediatric patients with hemophilia A demonstrated a favorable risk benefit profile to recommend regular approval.

3. Post-Marketing Requirements

The long-term follow-up Study LTS16294 should be submitted for review once available.