Taiwan Food and Drug Administration

Assessment Report

Trade Name：允達安輸注液 / ROCTAVIAN solution for infusion

Active Ingredient：Valoctocogene roxaparvovec

License Number：MOHW-BI 001255

Applicant：美商百傲萬里生技股份有限公司台灣分公司

Approval Date：2024.03.15

Indication：
適用於治療嚴重 A 型血友病 (先天第八凝血因子缺乏) 之成人病人，必須沒有第八凝血因子抗體病史，且沒有可檢測到的第 5 血清型腺相關病毒(AAV5)抗體。

ROCTAVIAN is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).

Background Information

Trade Name	允達安輸注液 / ROCTAVIAN solution for infusion
Active Ingredient(s)	Valoctocogene roxaparvovec
Applicant	美商百傲萬里生技股份有限公司台灣分公司
Dosage Form & Strengths	注射液劑 2E13 vg/mL
Indication	適用於治療嚴重 A 型血友病 (先天第八凝血因子缺乏) 之成人病人，必須沒有第八凝血因子抗體病史，且沒有可檢測到的第 5 血清型腺相關病毒(AAV5)抗體。 ROCTAVIAN is indicated for the treatment of severe haemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).
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Pharmacological Category **ATC Code**	B02BD02

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Valoctocogene roxaparvovec is a rAAV5-based gene therapy containing the cDNA of the B domain deleted SQ form of human coagulation factor VIII gene (hFVIII SQ) under the control of a liver specific promoter. It is produced in a baculovirus expression system that derived from cells of *Spodoptera frugiperda* (Sf9 cell line).

Manufacturing

The manufacturing process of DS consists of cell expansion, infection, harvest, purification and filtration. A production run begins with cell bank vial thawed, through the cell culture expansion, infection with recombinant baculovirus, harvest treatment, followed by a series of purification steps. The material is then formulated resulting in formulated bulk drug substance (FBDS).

Controls

- Sufficient details are provided on the source and history of the cell substrate. The generation of the production cell line and the genetic material are described in detail.
- The details of raw and starting materials used in the manufacturing process as well as quality standards (compendial monograph or in-house specifications) are presented.
- The in-process controls and critical process parameter are provided sufficiently.
- The result of the virus clearance study is considered acceptable.
- The risk for transmission of TSE/BSE is inferred to be negligible.

Process validation

The validation of the manufacturing process was carried out on full-scale PPQ lots. Results obtained from these batches meet the pre-defined criteria and demonstrate the process consistency.

Characterization

The followings are included in characterization studies：

- Physicochemical properties and strength.
- Biological characterization: titer and potency.
- The potential product- and process-related impurities have been analyzed and are considered sufficiently controlled.

DS specification

The release testing of the DS includes identity, quality, purity, potency, strength, safety and compendial tests. Reports of the non-compendial analytical procedures validations are provided. The proposed specifications of DS are considered adequate and acceptable.

Reference materials

The RSs have been established for release, stability and in-process testing, and the qualification data have been provided.

Stability

The stability data from production batches revealed that the DS is stable under storage condition at −70±10°C.

2.1.2 Drug product

The DP is available as a sterile 1.6×10^{14} vector genomes (vg)/ 8 mL solution for infusion,

packaged in glass vial. The excipients for DP solution contain Disodium phosphate dodecahydrate, Mannitol, Sodium chloride, Sodium dihydrogen phosphate dihydrate, Poloxamer 188, and water for injection.

Manufacturing

The manufacturing process consists of receipt of FBDS, sterile filtration, followed by an aseptic filling into sterile vial. The manufacturing process description is adequate.

Controls

The critical process parameters and in-process control tests have been provided properly.

Process validation and/or evaluation

The process validation summaries on production batches are provided. The aseptic processing and the suitability of the equipment are ensured.

DP Specification

The release testing of the DP includes identity, quality, purity, potency, strength, safety and general tests of physicochemical properties. The proposed specifications of DP are considered adequate and acceptable. Batch analysis data of finished product batches are provided, and the results reveal a satisfactory batch to batch consistency.

Reference materials

The RSs are the same as used to test the DS.

Stability of the DP

The long-term and accelerated stability data for DP are provided.

The photostability, and in-use studies were also performed on DP batches. Overall, the stability data provided could support the proposed shelf-life of 48 months when the DP is stored at the recommend condition (≤ -60°C). A post-thaw time hold in the intact DP vial (stopper not yet punctured) when stored at 2–8°C has also been set at 3 days, upright and protected from light. The in-use stability results showed that the DP are stable for 10 hours at 25°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Primary pharmacodynamic studies showed that transduction with increasing vector doses resulted in a dose-dependent increase in hFVIII-SQ RNA and protein in multiple species. In functional assessment, BMN270 dose-dependently improved the coagulopathy which was comparable to exogenously administrated Xyntha® in the mouse model of hemophilia A. In all general safety studies, animals were subjected to daily in-life clinical observations, and BMN270 is not expected to impact major organ systems (i.e., CNS, CV, Respiratory) function.

In biodistribution studies in mice and monkeys, the vector RNA was predominantly expressed in the liver and low expressed or not detectable in other tissues in a 26-week observation period. It should be noted that the time required for complete clearance remains unknown. In GLP-compliant germline transmission studies, no transgene DNA was detected in F1 pups in immune-deficient mice, indicating the likelihood of germline transmission is low. In immunity studies, pre-existing neutralizing antibodies may reduced the transduction efficiency in monkeys, but the efficacy remained. The integration frequency of engineered AAV vectors is orders of magnitude lower than the spontaneous rate of mutation for human genomes, so the likelihood of insertional mutagenesis is low.

2.2.2 Toxicological Studies

BMN270 was evaluated in GLP-compliant single-dose toxicity studies in mice for a 26-week observation duration via IV bolus administration, which is similar to clinical ROA (IV infusion) and consistent with proposed dose regimens. Toxicity findings were those known potentially species-specific immune responses attributed to the heterologous nature of exogenous factor replacement, possibly as a result of the formation of antibodies against human FVIII that cross-reacted with endogenous FVIII in immune-competent animals with the intact coagulation system. These antibodies cross-reacted with endogenous FVIII in mice, leading to a loss of endogenous FVIII activity, APTT prolongation, visceral lesions associated with hemorrhage in multiple organs (i.e., lung, heart, thymus, and epididymis), and even morbidity or mortality at $\geqq$6E13 vg/kg in 26-week observation study. APTT prolongation was also noted in the non-GLP monkey studies. These immunogenicity outcomes are not expected to translate to hemophilia A patients in the clinic.

Of note, no clear BMN270-related effects on liver function were noted in either immune-competent mice or monkeys administrated up to 2E14 vg/kg. In the INF-gamma ELISpot assay, anti-AAV5 TAbs were detectable but associated cellular immune responses were not noted in monkeys. Genotoxicity, carcinogenicity, and reproductive studies were not conducted. Instead, the applicant provided the appropriate and acceptable justification based on the biological attributes, the current scientific publication, and the pharmacology and toxicology data.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Traditional pharmacokinetic analyses do not apply to products that form in vivo, and therefore no clinical studies have been conducted to investigate the classical aspects of absorption, metabolism or excretion of ROCTAVIAN. No traditional clinical studies related to various intrinsic and extrinsic factors were conducted.

ROCTAVIAN transgene DNA levels (total amount of vector DNA) in various tissues (evaluated in nonclinical studies), blood, and shedding matrices were determined using a quantitative polymerase chain reaction (qPCR) assay. This assay is sensitive to transgene DNA, including fragments of degraded DNA. It does not indicate whether DNA is present in the vector capsid, in cells or in the fluid phase of the matrix (e.g., blood plasma, seminal fluid), or whether intact vector is present. Plasma and semen matrices were further evaluated by measuring encapsidated (potentially infectious) vector DNA using an immunoprecipitation quantitative PCR assay in Studies 270-201 and 270-301.

In preclinical study, biodistribution of ROCTAVIAN was assessed in adult male mice. Following intravenous administration of 6.0×10^{13} vg/kg or 2.1×10^{14} vg/kg, vector DNA was detected in all tissues, bone marrow, and blood analyzed at day 28, 91 and 182. The highest vector DNA concentration was detected in the liver, followed by lower levels in the lung, heart, lymph nodes, kidney, spleen, bone marrow, testis, and brain through six months post-administration. The levels of vector RNA for the tissues, blood and bone marrow samples analyzed from 6.0×10^{13} vg/kg and 2.1×10^{14} vg/kg dose group at day 28, day 91, and day 182, were detected predominantly in the liver with low (<1% relative to liver) or no expression in other tissues or sample types.

In clinical studies (Study 270-201 and Study 270-301), following 6.0×10^{13} vg/kg dose, median peak vector DNA levels were greatest in blood followed by saliva, semen, stool, and urine. The peak concentrations observed between 1 and 9 days post-administration. The peak concentration observed to date in blood across was 2×10^{11} vg/mL. The maximum concentration in any shedding matrix was 1×10^{10} vg/mL. After reaching the maximum in a matrix, the transgene DNA concentration declines steadily. After 6.0×10^{13} vg/kg administration, 100%, 100%, 89% and 100% participants had 3 consecutive BLQ or negative measurements in saliva, semen, stool, and urine in the both studies. The maximum time to the first of 3 consecutive LLOQ measurements was 52 weeks for saliva, 36 weeks for semen, 131 weeks for stool and 8 weeks for urine. In the evaluable patients from studies 270-201 and 270-301, encapsidated (potentially infectious) vector DNA was detectable in plasma and semen

was up to 10 weeks and 12 weeks after administration. Magnitude and duration of shedding appear to be independent of the patient's attained factor VIII activity.

In studies 270-201 and 270-301, all patients receiving treatment were required to screen negative for anti-AAV5 antibodies and negative (< 0.6 BU) for factor VIII inhibitors in a Nijmegen modified Bethesda assay following a lifetime minimum of 150 exposure days to factor VIII replacement therapy. Following infusion of ROCTAVIAN, all patients remained negative for factor VIII inhibitors at all time points evaluated post-infusion by the time of the data cut. All patients seroconverted to anti-AAV5 antibody positive within 8 weeks of administration. Mean anti-AAV5 total antibody titres peaked by 36 weeks after administration and remained stable until the last time point tested. ROCTAVIAN-treated patients were tested for cellular immune responses against the AAV5 capsid and the factor VIII transgene product using an IFN-γ ELISpot assay. AAV5 capsid-specific cellular immune responses were associated with higher mean ALT values at matched timepoints. Factor VIII-specific responses were detected in fewer subjects, often sporadically at a single time point and reverting to negative in most patients. No association between factor VIII cellular immune response and ALT or factor VIII activity measures could be detected.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The Applicant provided a pivotal phase III study, 270-301, for treatment in male subjects with severe Hemophilia A to claim the efficacy and safety of BMN 270.

When comparing efficacy of the primary endpoint "the change in the hFVIII activity post-BMN 270 infusion from baseline" before and after the treatment during Weeks 49-52, significant improvement can be found with estimated difference = 41.78 (p-value < 0.0001); while that at Week-104 with estimated difference = 22.04 (p-value < 0.0001). Subgroup, sensitivity and secondary efficacy analyses coincided with the main analysis result.

The update 3-year efficacy analyses demonstrated consistent results although the hFVIII activity level declined gradually with estimated difference at Week-156 = 17.41. The mean annualized treated bleeding rate decreased from 4.83 to 0.83, and was generally stable during each year after BMN 270 infusion.

2.4.2 Safety Results

The safety data were mainly based on the 170 subjects with severe hemophilia A who received any dose of BMN 270; the majority (160 [94.1%]) subjects were AAV5 total binding antibody

negative and received BMN 270 at the dose of 6×10^{13} vg/kg.

All but one (99.4%) subjects experienced at least 1 treatment emergent adverse event (TEAE). The most commonly reported TEAE were ALT increased (87.1%), arthralgia (44.1%), headache (42.4%), AST increased (35.9%), nausea (34.1%), fatigue (28.8%), acne (25.9%), upper respiratory tract infection (25.3%), nasopharyngitis (24.1%), pyrexia (22.9%), diarrhea (21.8%), insomnia (21.8%), COVID-19 (20.6%), back pain (20.6%), and oropharyngeal pain (20.0%).

Sixty (35.3%) subjects reported at least 1 Grade ≥ 3 TEAEs. The most common Grade 3 TEAE was ALT increased. Five subjects reported 8 Grade 4 TEAEs and 1 subject reported 1 Grade 5 TEAEs. All these Grade 4 or Grade 5 TEAEs were assessed as not related to BMN 270.

Forty-one (24.1%) subjects reported serious TEAEs, and the most common serious TEAE was rectal hemorrhage. No subjects required permanent termination of valoctocogene roxaparvovec infusion prior to completion or withdrew from study due to TEAEs.

Inflammatory response with ALT elevations was anticipated and occurred most frequently in the first 26 weeks post BMN 270 infusion. In a majority of subjects, ALT elevations responded rapidly to corticosteroid initiation.

Eleven (6.5%) subjects experienced at least 1 TEAE meeting the criteria for hypersensitivity reactions, including 1 subject with serious Grade 3 anaphylactic reaction.

No subjects with FVIII activity > 150 IU/dL had TEAEs suggestive of thromboembolic events. No subject developed a clinically relevant FVIII inhibitor.

One event of acinic cell carcinoma of the parotid gland and one event of B-ALL were reported. Both events were assessed as unrelated to BMN 270.

2.5 Bridging Study Evaluation

Considering the MOA of ROCTAVIAN, ethnic difference was not concerned in PK aspect. The models for E_{max}, and $E_{avg0\text{-}104w}$ identified race as having a potential association with FVIII activity. The observed treatment response of subjects in Africa region was lower, while FVIII activity was similar between subjects in North America, Europe and East Asian. Therefore, ethnic difference was not concerned in PD aspect.

Study 270-301 enrolled 19 Asian subjects, including 10 subjects from Taiwan and 1 subject from Korea. The efficacy and safety data from these 19 Asian subjects or 10 Taiwanese subjects

were consistent with the overall population.

2.6 Conclusion

Based on the above multidiscipline review, CDE review team leader recommends approval of Valoctocogene roxaparvovec (BMN 270).

1. Recommended Indication: Treatment of severe hemophilia A (congenital factor VIII deficiency) in adult patients without a history of factor VIII inhibitors and without detectable antibodies to adeno-associated virus serotype 5 (AAV5).
2. Recommended dose: 6×10^{13} vector genomes per kilogram (vg/kg) body weight, administered as a single intravenous infusion.
3. Under the recommended storage condition of ≤ -60℃, the shelf-life for valoctocogene roxaparvovec is 48 months.

3. Post-Marketing Requirements

1. Submit the clinical study report (CSR) of the following trials once available:
   (1) Study 270-801, including Taiwanese patients.
   (2) Study 270-201
   (3) Study 270-205
   (4) Study 270-301
   (5) Study 270-303
   (6) Study 270-401
   (7) Study 270-601
2. Taiwan Risk Management Plan (RMP)