Taiwan Food and Drug Administration

Assessment Report

Trade Name：諾健生靜脈懸液注射劑/
Zolgensma Suspension for Intravenous Infusion

Active Ingredient：Onasemnogene abeparvovec

License Number：MOHW-OBI 000029

Applicant： 台灣諾華股份有限公司

Approval Date：2020/12/22

Indication：
治療 6 個月以下經基因確診之 SMA 脊髓性肌肉萎縮症病人，其 SMN2 為 2 或 3 套或已出現症狀之 SMA 第一型病人，但不適用於已使用呼吸器每天 12 小時以上且連續超過 30 天者。

Treatment of patients less than 6 months of age diagnosed with spinal muscular atrophy (SMA) and 2 or 3 copies of SMN2 confirmed by a genetic testing, or who has been diagnosed with symptomatic SMA Type 1, but not applicable to patients who have been used ventilator for more than 12 hours a day and more than 30 consecutive days.

Background Information

Trade Name	諾健生靜脈懸液注射劑/ Zolgensma Suspension for Intravenous Infusion
Active Ingredient(s)	Onasemnogene abeparvovec
Applicant	台灣諾華股份有限公司
Dosage Form & Strengths	Suspension for Intravenous Infusion 2.0×10^{13} vector genomes (vg) / mL
Indication	治療 6 個月以下經基因確診之 SMA 脊髓性肌肉萎縮症病人，其 SMN2 為 2 或 3 套或已出現症狀之 SMA 第一型病人，但不適用於已使用呼吸器每天 12 小時以上且連續超過 30 天者。 Treatment of patients less than 6 months of age diagnosed with spinal muscular atrophy (SMA) and 2 or 3 copies of SMN2 confirmed by a genetic testing, or who has been diagnosed with symptomatic SMA Type 1, but not applicable to patients who have been used ventilator for more than 12 hours a day and more than 30 consecutive days.
Posology	For single-dose intravenous infusion only. Patients will receive a dose of nominal 1.1×10^{14} vg/kg onasemnogene abeparvovec. The total volume is determined by patient body weight.
Pharmacological Category ATC Code	M09AX09

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

AVXS-101 is a non-replicating, recombinant adeno-associated virus serotype 9 (AAV9) containing the human survival motor neuron (SMN) gene under the control of the cytomegalovirus (CMV) enhancer/chicken-β-actin-hybrid promoter (CB). One of the two adeno-associated vector (AAV) inverted terminal repeats (ITRs) has been modified to promote intramolecular annealing of the transgene, thus forming a double-stranded transgene ready for transcription. Through the AVXS-101 manufacturing process, this vector construct sequence is encapsidated into AAV9 virions.

Manufacturing

The AVXS-101 DS is manufactured at AveXis, Inc., USA, in accordance with cGMPs. The process of AveXis, Inc. DS consists of three key steps, including the upstream cell culture, downstream purification process and the final filtration and storage process, which has been described in sufficient detail with the accompanied process flow diagrams.

A production run begins with the WCB vial thawed, through the cell culture expansion and harvest of the production culture and purification by a series of chromatography steps. Additional steps are introduced for inactivation and removal of the potential viral contaminants. The DS solution is then adjusted to its final formulation and filtration into the storage bags resulting in the DS batch indicated.

Controls

The construction of expression vector and generation of the cell substrate have been described in details. The source and history of the host cell line were provided. The in-process controls, including the microbial controls, performance attributes, and critical process parameters were provided.

Process validation

The Process Performance Qualification (PPQ) component of Process Validation for AVXS-101 DS was performed at the commercial production scale at AveXis Libertyville and was designed to achieve initial qualification of the routine production process. The AVXS-101 DS manufacture process was qualified in three stages. The results for the PPQ batches, along with an evaluation met the pre-defined acceptance criteria.

Manufacturing process development

During the DS manufacturing process development (changed from process A (phase I) to process B (phase III)), the process changes or improvements were implemented.

Based on the comparability studies, the resulting quality attributes from the Phase 1 clinical drug product using Process A and AVXS-101 Phase III clinical, Preprocess performance qualification (PPQ), and representative commercial lots from Process B were found to be comparable. The data evaluation also demonstrated the consistency of AVXS-101 Process B manufacturing.

Characterization

As part of the AVXS-101 characterization, a series of experiments combining SDS-PAGE analysis, genomic isolation, SMN expression analysis by in vitro transduction, residual DNA analysis, genomic titer analysis, total protein content, and analytical ultracentrifugation (AUC) were performed to demonstrate the quality attributes of AVXS-101.

DS specification

The release testing of AVXS-101 DS includes appearance (color and clarity), pH, identity, osmolality, purity, impurity, quantity and contaminants. These tests are performed either according to pharmacopeial methods or by in-house analytical methods. Descriptions of the non-pharmacopeia analytical procedures validation summaries have been provided. The proposed specifications of DS are considered adequate and acceptable.

Reference materials

The reference standards used in the testing and release of AVXS-101 DS is the same as the one used for the testing and release of AVXS-101 DP.

Stability

Several full-scale AVXS-101 DS lots were placed on stability at the long-term storage condition of ≤ -60℃. The results indicate the stability of AVXS-101 DS at < -60℃.

2.1.2 Drug product

Each 1 mL of AVXS-101 DP solution in water for injection contains tromethamine (Tris), magnesium chloride, sodium chloride, and Poloxamer 188. AVXS-101 DP is filled into 10 mL vials.

Manufacturing

AVXS-101 DP vials are manufactured and released at AveXis, Inc. in USA. The manufacture process consists of DS thawing and pooling, sterile filtration and concentration adjustment, as well as aseptic filling, stoppering, capping, visual inspection, labelling and secondary packaging.

Controls

The critical process parameters, key process parameters, in-process control tests that control the critical steps at AveXis, Inc. have been provided.

Process validation

The PPQ results for the AVXS-101 DP manufacturing steps met the pre-established acceptance criteria stated in the prospective PPQ protocol. Therefore, the AVXS-101 DP manufacturing process, including steps to adjust for product concentration prior to the final sterile filtration step, has been found suitable to consistently produce material meeting critical quality attributes of the final product.

DP Specification

The specifications for AVXS-101 DP include general test, quantity, identity, potency, purity/impurities, sterility and container closure integrity. Many lots of AVXS-101 DP were provided and all comply with the specifications in place at the time of release as presented.

Reference materials

Primary reference standard was qualified using tests and acceptance criteria based on release specifications in place at the time of manufacture. The primary reference standard was bridged to the clinical material, as a part of reference standard qualification. Method specific qualification testing was performed to further assess including SDS-PAGE, Western Blot, in-vitro Relative Potency, and *in-vivo* Functionality assays. Subsequently, the primary reference standard was bridged to the clinical material through a side-by-side comparability study.

Stability of the DP

Stability studies for AVXS-101 DP are performed at long-term (≤ -60℃), accelerated (2 – 8℃), and stressed (20 – 25℃) conditions. Overall, the stability data provided could support the proposed shelf-life when the DP is stored at the recommend condition (≤ -60℃).

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

In the Spinal Muscular Atrophy (SMA) murine model, single intravenous (IV) administration of AVXS-101 improved the animals' survival, motor function, neuromuscular electrophysiology, body weight gain, and cardiac function. The optimal survival was observed on mice being dosed between the ages of P0−2 and at a minimum vector dose of 6.7 E13 vg/kg.

Following intravenous administration in the neonatal FVB mice, vector and transgene were widely distributed, and the highest expression was observed in the heart. High expression levels were also detected in the liver, lung, lymph node, masseter muscle (injection site), quadriceps muscle, and spinal cord. The lowest expression levels were detected in the spleen and gonad samples. The expression levels remained high at all time points and detectable in most samples, indicating the persistence of AVXS-101 DNA for the 24-week duration.

2.2.2 Toxicological Studies

In pivotal GLP compliant 3-month mouse toxicology studies, the main target organs of toxicity were the heart and liver. The additional finding included lung (perivascular and chronic inflammation) at ≥2.4E14 vg/kg. The cardiac findings were dose-related and presented at ≥7.9E13 vg/kg (mononuclear cell inflammation, edema, fibrosis, and scattered myocardial cell degeneration/regeneration). Additional cardiac findings at dose ≥1.5E14 vg/kg included atrial thrombosis and atrial dilation. Atrial thrombosis was often attributed as the cause of death (at a dose of ≥2.4E14 vg/kg, approximately 2.2-fold higher than the recommended clinical dose level) in unscheduled sacrifice animals and was considered potentially life-threatening. The pathogenesis of these atrial findings and the potential translatability to humans is unclear. The cardiac findings warrant further investigation and intense monitoring in clinical use. The pathogenesis of AVXS-101-related liver findings has not been specifically studied but is likely related to an innate and/or acquired immune response to the viral capsid and/or transgene product, which is prominently distributed to the liver. In clinical trials, transient abnormalities in liver function tests have commonly been observed and are likely correlated with these preclinical findings. Although this represents a narrow therapeutic index, the reproducible and clinically translatable safety profile provides proper guidance on clinical risk and appropriate safety monitoring. The benefit and risk profile are considered favorable, given the profound clinical benefit in the severe and life-threatening disease and the toxicity's monitorable and manageable nature.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Conventional clinical pharmacokinetic (PK) studies are not applicable to gene therapy products. In lieu of conventional PK studies, the excretion of AVXS-101 was estimated by measuring shed virus consistent with the General Principles to Address Virus and Vector Shedding.

The bioavailability of AVXS-101 in the systemic circulation is assumed to be 100% when delivered via IV infusion. The precise bioavailability in CNS has not been studied in human, but the transduction efficiency of CNS neurons has been studied in mice and nonhuman primates.

Samples of saliva, urine, and stool were collected at weekly time points through Day 30 and then monthly time points through Month 12 and every 3 months thereafter. Samples from 5 patients were used for viral shedding analysis through the Month 18 visit. Data from 5 patients (the 5 patients used were the highest weight patients that received the highest viral doses) were considered to adequately characterize viral shedding.

All 5 patients analyzed for viral shedding were dosed with the proposed therapeutic dose. AVXS 101 was detectable in shed samples post-infusion. AVXS 101 concentrations in urine and saliva were 0.1% to 0.01% of initial concentration in the body at day 1 post infusion, after which concentrations fell below the limit of quantitation. In stool, levels 10% to 30% of the initial concentration in the body were detectable at day 1 post infusion. One patient showed a peak concentration in stool at day 14 post infusion of 280% of initial concentration in body. In contrast, three patients for whom data were available showed a concentration of <1% of initial concentration in body at day 14 post infusion, with concentrations declining approximately 4 logs (10,000-fold) over 30 days post infusion.

Overall, AVXS 101 was primarily cleared from the body in stool and by day 60 post infusion was below the limit of quantitation in stool. Shed AAV vectors have been previously shown not to be infectious in urine and saliva excreta. Together, these data demonstrate rapid decline of shed vector quantities well below initial concentrations in patients treated with AVXS-101. Clearance of AVXS-101 is primarily via the feces and the majority of the dose is cleared within 30 days of dose administration.

Immune response to AVXS-101 was also assessed for development of anti-AAV9 antibodies or anti-hSMN antibodies (ELISA) and also the T-cell response to AAV9 and SMN peptides (ELISpot). Although all patients had increases in anti-AAV9 antibodies, there were no apparent differences in either safety or efficacy, based on these results.

Exploratory pharmacodynamic measures (compound muscle action potential [CMAP] and motor unit number estimation [MUNE]) were included in Study CL-101. Overall, the effects of AVXS-101 on CMAP and MUNE are supportive of the overall clinical efficacy observed in the study.

AVXS-101 is primarily cleared via the feces with majority cleared by Day 30, and levels of AVXS-101 undetectable after 60 days post dose. There is no apparent relationship between immunogenic response and safety and efficacy. Improvements in CMAP and MUNE observed in the study are supportive of the overall efficacy conclusions; greater improvements in CMAP and MUNE were observed in patients who received the proposed therapeutic dose. AVXS-101 met the minimum regulatory requirement, hence the approval is recommended.

2.4 Clinical Efficacy and Safety Evaluation

The clinical efficacy and safety data for intravenous administrated Zolgensma primary comes from 3 interventional studies (CL-101, CL-303 and CL-304) and one long-term observational study (LT-001).

2.4.1 Efficacy Results

The phase 1 study CL-101 was an open label, single infusion, ascending dose, single center study in up to 15 patients with Type 1 SMA. Three patients received low dose 6.7E13 vg/kg and 12 patients received high dose 2.0E14 vg/kg. Both cohorts had statistically significantly improved survival without permanent ventilation as compared with the PNCR natural history estimate. Patients in high dose cohort achieved significant motor milestones never seen in the natural course of disease. As no patients in low dose cohort achieved a significant motor milestone, dose-response in efficacy was observed. High dose 2.0E14 vg/kg by qPCR, which is equivalent to therapeutic dose 1.1E14 vg/kg by ddPCR due to different quantitative assay, was selected for the phase 3 studies. All of the 10 patients from high dose cohort who entered the long-term study LT-001 could maintain and/or develop new milestones up to the age from 51.3 months to 67.5 months.

The pivotal phase 3 Study CL-303 was an open label, single arm, single dose study in patients with SMA Type 1 with 1 or 2 copies of SMN2 and < 6 months of age at the time of gene replacement therapy. All patients received a single dose of Zolgensma at 1.1E14 vg/kg via IV infusion. Thirteen (13) of 22 patients (59.1%) were able to sit independently for 30 seconds at 18 months of age (p-value < 0.0001, co-primary endpoint H0: $p_{Zolgensma}$=0.1%). The mean (SD) age of achieving this milestone was 12.91(2.943) months of age. Twenty patients (90.9%) had survived event free to ≥ 13.6 months of age. Zolgensma has significant therapeutic benefit in prolonging survival without permanent ventilation compared to natural disease history of 25% at 13.6 months of age (p-value < 0.0001, co-primary endpoint).

Study CL-304 was a Phase 3, open-label, single-arm, single-dose trial for the treatment of pre-symptomatic newborn patients expected to develop SMA with bi-allelic SMN1 deletions and 2 or 3 copies of SMN2 who are ≤ 6 weeks of age at the time of gene replacement therapy. Fourteen patients had 2 copies of SMN2, 15 patients had 3 copies of SMN2, and 1 patient had 4 copies of SMN2 were enrolled. As of the data cutoff date 31 Dec 2019, 8 of 14 (57.1%) patients in the 2-copy SMN2 cohort had achieved the video-confirmed primary efficacy endpoint of sitting without support for 30 seconds. Four of 15 (26.7%) patients in the 3-copy SMN2 cohort had achieved the video-confirmed primary efficacy endpoint of standing without support according to the Bayley Scales definition.

In summary, Study CL-101 (high-dose cohort) and Study CL-303 in subjects with SMA Type 1 demonstrated sufficient evidence for the efficacy of Zolgensma 1.1E14 vg/kg single IV injection compared with historical controls in survival and milestone achievement. In addition, Study CL-304 in subjects with pre-symptomatic SMA and 2 or 3 copies of SMN2 also provided evidence for the efficacy of Zolgensma 1.1E14 vg/kg single IV injection in highest motor milestone achievement.

2.4.2 Safety Results

As of the data cutoff date 31-Dec-2019, 97 patients received one-time IV administration of Zolgensma. Across all studies, 96 of 97 (99.0%) patients had at least one TEAE and almost half (46.4%) patients had at least one serious TEAE. The most common (incidences ≥20%) TEAEs were pyrexia (48.5%), upper respiratory tract infection (37.1%), vomiting (24.7%), constipation (22.7%), and cough (20.6%). The most common (incidences ≥5%) serious TEAEs were respiratory distress (7.2%), and upper respiratory tract infection (6.2%). Two patients died due to respiratory arrest and respiratory distress/ hypoxic-ischemic encephalopathy respectively during study.

Both cases were considered unrelated to Zolgensma by the investigator.

Important identified risk included hepatotoxicity and transient thrombocytopenia. The elevation in liver transaminases is manageable with the prednisolone regime used in the clinical trials. No patient met criteria for Hy's Law. Thrombocytopenia was transient and without clinical significance. Important potential risks included cardiac adverse events and dorsal root ganglionopathy (DRG). Both were identified in animal studies and needed further observation.

2.5 Bridging Study Evaluation

Zolgensma is a certified Rare Disease Drug (罕見疾病藥物). No formal submission of Bridging Study Evaluation is required according to the regulation in Taiwan. However, from the PK point of view, considering the MOA of Zolgensma comes from supplement of endogenous protein and its IV administration route, ethnic difference was not concerned.

2.6 Conclusion

The review team recommends approval of Zolgensma under regular approval for the treatment of pediatric patients less than 6 months of age with bi-allelic mutations in the survival motor neuron 1 (SMN1) gene and with symptomatic spinal muscular atrophy (SMA) type 1, or 2 to 3 copies of SMN2 gene. Considering the limitation of clinical benefits in patients with advanced SMA (e.g., ventilator dependence), the indication would be restricted to patient without ventilator dependence.

3. Post-Marketing Requirements

Risk Management Plan (RMP) of Zolgensma after marketing approval was requested during the review process. The proposed methods to conduct the RMP include Medication Guide, Communication Plan, Product Registry, Educations for company employee, and Routine Pharmacovigilance Activities. The RMP report will include the product registry study report in every 2 years.