November 16, 2022
Pharmaceuticals and Medical Devices Agency

Errata Sheet for Revisions to Review Report

Brand name ZOLGENSMA Intravenous Infusion
Non-proprietary name Onasemnogene abeparvovec
Applicant Novartis Pharma K.K.
Date of application November 1, 2018

The following revisions are made to the Review Report dated February 7, 2020 for the above-mentioned product because a paper reporting the results of a non-clinical study which had been addressed in the Review Report (1) was retracted by the editors of the journal on October 6, 2022. These revisions, however, do not affect the overall results of the review, as clinical study data have demonstrated the efficacy and safety of the product.

Page No.	Row No.	Before revision	After revision
13	23	Texts before and after revision are shown under this table.	
61	13	The applicant's explanation about the basis for the proposed dosage and administration or method of use: In an *in vivo* study in SMNΔ7 mice, a single intravenous administration of scAAV9.CBA.SMN vector at dose levels of 6.7×10^{13} and 3.3×10^{14} vg/kg resulted in survival of approximately 35 and 250 days, respectively, while mice injected with scAAV9.CB.GFP vector had a median survival of 15.5 days [see Section 4.1]. scAAV9.CBA.SMN vector 6.7×10^{13} and 2.0×10^{14} vg/kg in mice were converted to human doses to determine the doses of Zolgensma for Cohorts 1 and 2 of Study CL-101. Since the clinical efficacy of Zolgensma	The applicant's explanation about the basis for the proposed dosage and administration or method of use: Since the clinical efficacy of Zolgensma was demonstrated in Cohort 2 of Study CL-101, the dosing regimen of Zolgensma was proposed based on Cohort 2 of Study CL-101.

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(Underline denotes revision.)

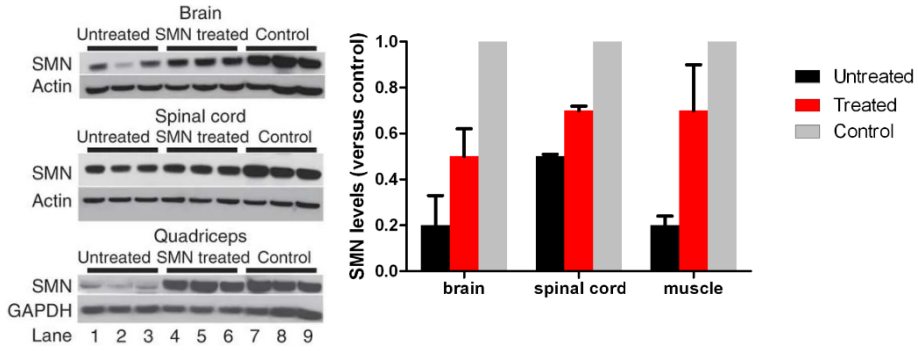
Before revision

4. Indication or Performance and Outline of the Review Conducted by PMDA

4.1 *In vivo* studies

In vivo pharmacology studies of Zolgensma conducted are shown in Table 10.

Table 10. Summary of *in vivo* studies

Study Title[*1]	Principal findings
AAV9 transduction efficiency study in P1 neonatal mice (*Nat Biotechnol*. 2009; 27: 59-65)	Following intravenous administration of scAAV9.CB.GFP vector (4×10^{11} vg) that expressed GFP (green fluorescent protein), instead of SMN protein, to neonatal C57BL/6 mice (postnatal days 1-2), >56% of neurons were transduced. On the other hand, following intravenous administration of scAAV9.CB.GFP vector (4×10^{11}-4×10^{12} vg) to adult mice (postnatal day 70), predominant glial transduction was observed. The percentage of transduced neurons ranged from 5% to 10%.
In vivo efficacy study in SMNΔ7 mice (*Nat Biotechnol.* 2010; 28: 271-4)	SMNΔ7 mice with a major phenotype of SMA (*Smn*$^{-/-}$, *SMN2*$^{+/+}$, *SMNΔ7*$^{+/+}$)[*2] (postnatal day 1) received intravenous injection of scAAV9.CBA.SMN vector*[3] (3.3×10^{14} vg/kg). Effects observed are described below. (1) Elevated levels of SMN protein expression in the brain, spinal cord, and muscle SMN protein levels were increased in the brain, spinal cord, and muscle in animals treated with scAAV9.CBA.SMN vector compared to untreated animals, but were still lower than controls (normal mice) (Figure 1).  **Figure 1. SMN protein expression in brain, spinal cord, and muscle** (2) Improvement of motor function (righting reflex) By Day 13, 90% of animals treated with scAAV9.CBA.SMN vector were able to right themselves,[*4] compared with 20% of scAAV9.CB.GFP vector-treated controls and 0% of untreated animals (Figure 2).

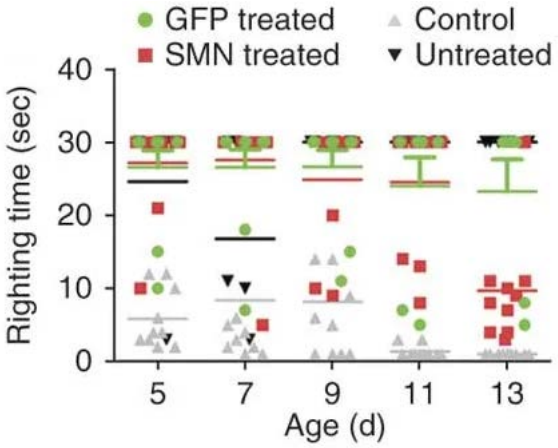


Figure 2. Righting time

(3) Prolongation of survival

Treatment with scAAV9.CBA.SMN vector resulted in extended survival over treatment with scAAV9.CB.GFP vector (Figure 3).

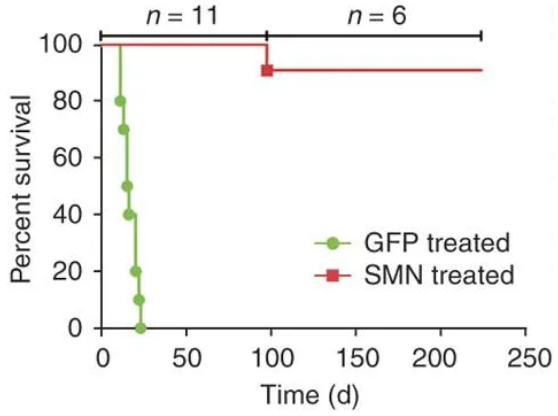


Figure 3. Survival

Furthermore, SMNΔ7 mice received intravenous injection of scAAV9.CBA.SMN vector (3.3×10^{14} vg/kg) on postnatal days 2 (P2), 5 (P5), and 10 (P10). Change in survival of P2-injected animals was indistinguishable from that of P1-injected animals, but P5-injected animals showed a more modest increase in survival. Survival of P10-injected animals was indistinguishable from that of scAAV9.CB.GFP vector-injected controls, and results showed no increase in survival (Figure 4).

SMNΔ7 mice received intravenous injection of scAAV9.CBA.SMN vector (1×10^{10} vg, 5×10^{10} vg, 1×10^{11} vg, 5×10^{11} vg[*5]) on postnatal day 1. Survival was increased at doses of $\geq1\times10^{11}$ vg (Figure 5).

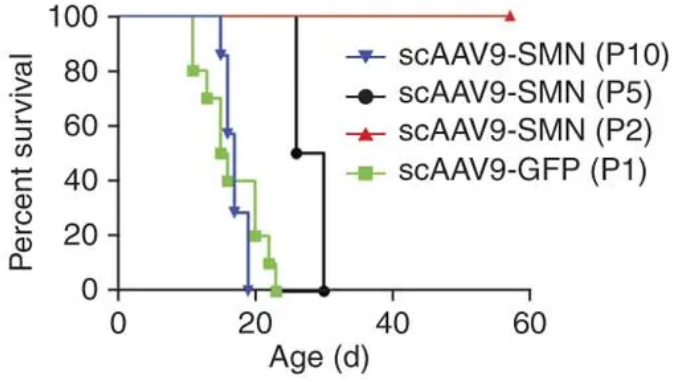
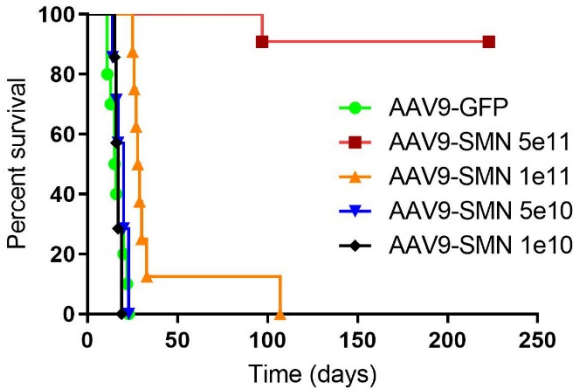


Figure 4. Age at time of injection and survival

	 **Figure 5. Dose-dependency of Zolgensma**
Transduction efficiency study in neonatal and juvenile monkeys (*Molecular Therapy*. 2011; 19: 1971-80)	Cynomolgus monkeys (postnatal days 1, 30, 90) received intravenous injection of scAAV9.CB.GFP vector (1-3×10^{14} vg/kg). Predominant neuronal transduction (approximately 70%) was observed.
Efficacy study using intrathecal delivery in a piglet model of SMA (*Ann Neurol*. 2015; 77: 399-414)	A model for SMA in piglets was generated by transducing piglets on postnatal day 5 with a short hairpin RNA (shRNA) construct targeting pig SMN to reduce endogenous SMN protein expression. Piglets on postnatal day 6 (pre-symptomatic SMA) received intrathecal injection of scAAV9.CBA.SMN vector (8×10^{12} vg/kg) but did not develop SMA signs or severe hind limb weakness during the period prior to euthanasia (6-10 weeks post-injection). On the other hand, in piglets intrathecally treated with scAAV9.CBA.SMN vector (2-3.8×10^{13} vg/kg) on postnatal day 33 to 36 (symptomatic SMA), partial amelioration of the disease*6 was observed by the time of euthanasia (6-10 weeks post-injection).

*1: The percent homology of the *SMN* mRNA sequence between humans and mice/pigs/cynomolgus monkeys was 84%, 89%, and 98%, respectively. The percent homology of the amino acid sequence of SMN protein between humans and mice/pigs/cynomolgus monkeys was 82%, 89%, and 97%, respectively.

*2: A mouse model of SMA. The SMNΔ7 mouse lacks the endogenous mouse *SMN* gene but carries human *SMN2* and *SMN2Δ7* (human *SMN2* with exon 7 removed).

*3: It has the same genome as the proposed product, but the comparability of quality attributes with those of the proposed product has not been demonstrated.

*4: The time taken for the mouse to reposition itself onto all four paws after being placed in a supine position. A cutoff of 30 seconds was used for failure to right.

*5: Equivalent to 3.3×10^{14} vg/kg

*6: Compound muscle action potential (CMAP) values were similar to values obtained in the control group (normal piglets) and the treated pre-symptomatic group. On postnatal day 54, motor unit number estimation (MUNE) in treated animals was not similar to that in the control animals (normal piglets), but was partially corrected with a value higher than in vehicle-injected animals.

4.R Outline of the review conducted by PMDA

The applicant's explanation about the effectiveness of Zolgensma in the treatment of SMA:

The results of *in vivo* studies demonstrated that when administered intravenously, scAAV9.CBA.SMN vector, which has the same genome as Zolgensma, infects the neurons of juvenile animals, leading to the expression of human SMN protein, and that the therapeutic vector improves motor function and survival. The studies also showed that early postnatal delivery of Zolgensma and its efficient neuronal transduction are important for achieving the optimal efficacy of Zolgensma.

PMDA accepted the applicant's explanation.

After revision

4. Indication or Performance

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