Important information regarding ZOLGENSMA® (onasemnogene abeparvovec-xioi) and the attached scientific reprint.

Day JW, Finkel RS, Chiriboga CA, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of *SMN2* (STR1VE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol.* 2021;20:284-293.

This reprint includes information about ZOLGENSMA that is not contained in the Prescribing Information. The information provided should in no way be construed as a recommendation for the use of this product in any manner other than as approved by the Food and Drug Administration and as described in the Full Prescribing Information for ZOLGENSMA.

Please note:

- This is the first publication of the findings of the Phase 3 trial (STR1VE) for ZOLGENSMA. STR1VE was an open-label, single-arm, multicentre trial conducted in the United States
- All patients treated in the study were symptomatic at the time of treatment and <6 months of age
- Results of the trial were consistent with findings from the Phase 1 trial (START), as well as demonstrating a significant improvement in survival and motor function in patients treated with ZOLGENSMA over the untreated natural history of patients with spinal muscular atrophy (SMA)
- Adverse events (AEs) were also consistent with the START trial

Indication and Important Safety Information

Indication

ZOLGENSMA is an adeno-associated virus vector-based gene therapy indicated for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the *survival motor neuron 1* (*SMN1*) gene.

Limitations of Use
The safety and effectiveness of repeat administration or the use in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated with ZOLGENSMA.

Important Safety Information

BOXED WARNING: Acute Serious Liver Injury and Acute Liver Failure
Acute serious liver injury, acute liver failure, and elevated aminotransferases can occur with ZOLGENSMA. Patients with preexisting liver impairment may be at higher risk. Prior to infusion, assess liver function of all patients by clinical examination and laboratory testing (e.g., hepatic aminotransferases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)], total bilirubin, and prothrombin time). Administer a systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion.

WARNINGS AND PRECAUTIONS

Thrombocytopenia
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Thrombotic Microangiopathy
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Elevated Troponin-I
Increases in cardiac troponin-I levels were observed following ZOLGENSMA infusion. Monitor troponin-I before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence ≥5%) in clinical studies were elevated aminotransferases and vomiting.

Please see accompanying Full Prescribing Information.

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Bannockburn, IL 60015

zolgensma®
(onasemnogene abeparvovec-xioi)
suspension for intravenous infusion

Onasemnogene Abeparvovec Gene Therapy for Symptomatic Infantile-onset Spinal Muscular Atrophy in Patients with Two Copies of *SMN2* (STR1VE): an Open-label, Single-arm, Multicentre, Phase 3 Trial

Day JW, Finkel RS, Chiriboga CA, et al. *Lancet Neurol.* 2021;20:284-293.

A Phase 3 trial of ZOLGENSMA® (onasemnogene abeparvovec-xioi) in the United States, also known as STR1VE, evaluated safety and efficacy in symptomatic infants <6 months of age with spinal muscular atrophy (SMA).[1]

ZOLGENSMA is the first and only gene therapy indicated for the one-time-only treatment of pediatric patients less than 2 years of age with SMA.[2,3]

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Study methods

Study design[1]

STR1VE was an open-label, single-arm, single-dose Phase 3 clinical trial conducted in the United States at 12 hospitals and universities.

Participants[1]

The study enrolled 22 patients, all of whom met the intent to treat (ITT) population:

- Presymptomatic or symptomatic[a]; <6 months of age at dosing
- Bi-allelic mutations of the *SMN1* gene
- One or two copies of the backup *SMN2* gene[b]
- Able to swallow thin liquids
- Up to date on childhood vaccinations

Patient demographics:

- **3.7** Mean age (months)
- **1.9** Mean age at symptom onset (months)
- **56.1** Mean age at diagnosis (days)
- **32.0** Mean CHOP INTEND score at baseline

[a]Although enrollment of presymptomatic patients was allowed in the study protocol, all patients included in the study were symptomatic at dosing.
[b]No patients with 1 copy of *SMN2* were enrolled, though it was included in the study protocol.

Procedures[1]

ZOLGENSMA was administered as a one-time intravenous infusion of 1.1×10^{14} vector genomes [vg]/kg for 30-60 minutes via a peripheral vein.

All patients received prophylactic prednisolone (1 mg/kg/day) beginning 24 hours before infusion and up to 30 days or more after infusion; tapering schedule was dependent on liver function test results.

Important Safety Information

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Study methods (cont'd)

Outcomes[1]

All endpoints were compared against a cohort of untreated infants with SMA from the Pediatric Neuromuscular Clinical Research Network (PNCR). Developmental milestones were assessed using independent, centrally reviewed video confirmation at any timepoint during the study.

Primary endpoints:

- Sitting independently for ≥30 seconds at the 18-months-of-age visit[a]
- Survival at 14 months of age[b]

Secondary endpoints:

- Ability to thrive at 18 months of age (ability to tolerate thin liquids, lack of nutritional support, and maintaining age-appropriate weight)
- Independence from ventilatory support at 18 months of age based solely on data from the Trilogy BiPAP device

Exploratory endpoints:

- Achievement of developmental motor milestones
- Sitting independently for 10 seconds or more
- Age at which independent sitting for ≥30 seconds was achieved
- Improvement of motor function using CHOP INTEND or Bayley scale criteria

[a]Functional, independent sitting for 30 seconds or longer as measured by Bayley-III item 26.

[b]Survival was defined as absence of death or permanent ventilation (tracheostomy or ≥16 hours of daily noninvasive ventilation support for ≥14 days in the absence of acute reversible illness or perioperative ventilation).

Safety[1]

Safety was assessed through adverse events (AEs), concomitant medications, physical examinations, vital sign assessments, cardiac assessments, and laboratory evaluations.

Important Safety Information

WARNINGS AND PRECAUTIONS

Thrombotic Microangiopathy

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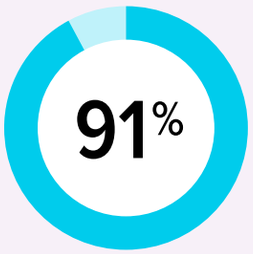
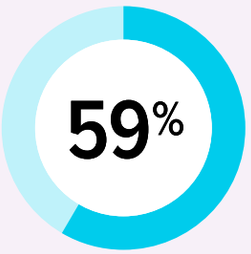
Clinical study results

Overview[1]

Primary endpoints

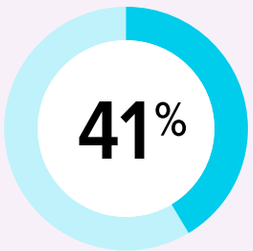


20/22 patients **survived without permanent ventilation** at the 14-months-of-age visit

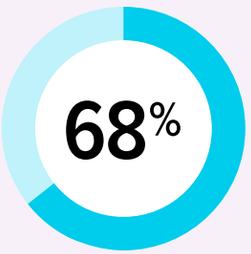


13/22 patients **achieved independent sitting for 30 seconds** at the 18-months-of-age visit

Secondary endpoints



9/22 patients **maintained the ability to thrive** at 18 months of age



15/22 patients **did not require noninvasive ventilatory support** at any point during the study

4/22 (18%) patients required ventilatory support as assessed by Trilogy BiPAP data alone at 18 months of age

Survival[1]

20/22 (91%) patients survived without permanent ventilation at 14 months of age.[a,b]

- Compared to 6/23 (26%) patients in the PNCR natural history cohort

Ventilatory support

15/22 (68%) of patients did not require noninvasive ventilatory support at any point during the study.

- Compared to 0/23 (0%) patients in the PNCR natural history cohort
- 4/22 (18%) patients required ventilatory support as assessed by Trilogy BiPAP data alone at 18 months of age
- 5/7 (71%) patients who used ventilatory support had previous use of Trilogy 100; 2 had used other types of noninvasive ventilation

[a]Two patients discontinued treatment before 14 months of age: one patient died at 7.8 months of age because of respiratory failure unrelated to treatment. Another patient withdrew consent at age 11.9 months after meeting the requirements for permanent ventilation.

[b]One patient withdrew because of a serious AE, respiratory distress, at age 18.0 months unrelated to treatment; however, this patient was alive and free of permanent ventilation and was included in study results as having survived without permanent ventilation at 18 months of age.

Ability to thrive[1]

9/22 (41%) patients met all 3 criteria of ability to thrive at the 18-months-of-age visit.

- Compared with 0/23 (0%) patients in the PNCR cohort
- 14/22 (64%) patients maintained age-appropriate weight
- 12/22 (55%) patients were able to tolerate thin liquids
- 19/22 (86%) patients were feeding orally at the end of the study

Important Safety Information

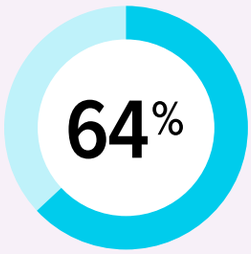
ADVERSE REACTIONS

The most commonly observed adverse reactions (incidence ≥5%) in clinical studies were elevated aminotransferases and vomiting.

Please see additional Important Safety Information and the accompanying Full Prescribing Information, including Boxed Warning.

Clinical study results (cont'd)

Motor milestones and function[1]



14/22 patients achieved sitting independently for 30 seconds at some point during the study.[a]

- Compared with 0/23 (0%) in the PNCR natural history cohort

Patients showed early and sustained improvements in CHOP INTEND assessments.

- 6.9 mean increase from baseline at 1 month post-dosing (N=22)
- 11.7 mean increase from baseline at 3 months post-dosing (N=22)
- 14.6 mean increase from baseline at 6 months post-dosing (n=20)

21/22 patients achieved a CHOP INTEND score of 40.0 points or more.

- 14/22 (66%) achieved a score of 50.0 points or more
- 5/22 (23%) achieved a score of 60.0 points or more
- In natural history, children with SMA Type 1 rarely achieve or maintain CHOP INTEND scores greater than 40 points

[a]One patient achieved this milestone at age 16.0 months; however, this milestone was not reconfirmed at the 18-months-of-age visit.

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WARNINGS AND PRECAUTIONS

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Adverse events[1]

22/22 (100%) patients had adverse events (AEs). The most common AE was pyrexia. A commonly observed AE related to ZOLGENSMA administration was elevations in liver aminotransferase concentrations.

- 12/22 (55%) patients had pyrexia
- 7/22 (32%) patients had elevations in aminotransferase concentrations or aspartate aminotransferase
- Transient increases of aminotransferases were all successfully resolved by the end of the study

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Three patients had serious AEs related to ZOLGENSMA.

- 2/22 (9%) patients had elevated hepatic aminotransferases
- 1/22 (5%) patients had hydrocephalus and received ventriculoperitoneal shunt placement

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Transient decreases in platelet count occurred in most patients after approximately a week post-dosing.

- All platelet counts returned to normal levels without a change in the prednisolone regimen
- Two patients had decreases in platelet counts that met the criteria for thrombocytopenia, which resolved without clinical sequelae

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13/22 (59%) patients had at least one adverse event of special interest within the 4 categories of hepatotoxicity, hematological, cardiovascular, or neurological.

Deaths in 2 patients were reported, which were both deemed unrelated to ZOLGENSMA administration.

- One death was due to respiratory distress. The other occurred at screening, and this patient was not enrolled in the study

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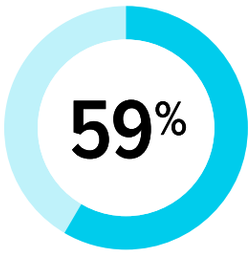
Conclusions

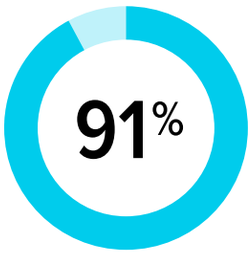
Authors' conclusions[1]

The STR1VE trial built on the efficacy and safety data of the Phase 1 START trial in symptomatic infants with SMA Type 1 and demonstrated a favorable benefit-risk profile with a larger (N=22 vs n=12), more diverse population (multicentre vs. single site).



13/22 patients—over half—treated in STR1VE achieved the primary endpoint of sitting independently for ≥30 seconds at the 18-months-of-age visit.

- Several patients achieved other exploratory endpoints, contrasting with the untreated natural history



20/22 patients survived without permanent ventilation at the 14-months-of-age visit.

Patients with SMA may have a predisposition to liver injury.[4]

- Consider hepatic evaluation in children with baseline elevated aminotransferase
- Avoid concomitant use of medications with hepatotoxic AEs

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Study summary[1]

- 22 patients with SMA Type 1 were enrolled in the Phase 3 study
- ZOLGENSMA showed results consistent with the Phase 1 study (START), as well as significant improvement compared to the PNCR natural history cohort
- Over half of patients reached the primary endpoints of sitting independently for ≥30 seconds at the 18-months-of-age visit and survival without permanent ventilation at the 14-months-of-age visit
- The reported AEs were consistent with results from the Phase 1 trial

The exploratory CHOP INTEND results showed early, rapid, and sustained benefits of ZOLGENSMA[1]

Learn more about the one-time-only treatment for SMA at ZOLGENSMA-hcp.com[2]

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