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

Waldrop MA, Karingada C, Storey MA, et al. Gene therapy for spinal muscular atrophy: safety and early outcomes. *Pediatrics*. 2020;146(3):e20200729.

This reprint includes information about ZOLGENSMA that is not contained in the Prescribing Information approved by the Food and Drug Administration (FDA). 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 FDA and as described in the Prescribing Information for ZOLGENSMA.

Please note:

- This is a retrospective review of the safety and early outcomes of ZOLGENSMA in 21 pediatric patients, aged 1-23 months, with SMA treated across 4 centers in Ohio
- The review includes patients who had previously been treated with nusinersen. The ZOLGENSMA clinical trials did not include any patients who had previously received disease-modifying therapy
- This review includes patients who were 8 months of age or older at the time of treatment with ZOLGENSMA. The ZOLGENSMA clinical trials did not include any patients treated after 8 months of age
- Recommendations and conclusions provided within the conclusion section are the authors' own

Indication and Important Safety Information for ZOLGENSMA (onasemnogene abeparvovec-xioi)

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
Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were typically observed within the first two weeks after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

Thrombotic Microangiopathy
Cases of thrombotic microangiopathy (TMA) were reported approximately 1 week after ZOLGENSMA infusion. Obtain baseline creatinine and complete blood count before ZOLGENSMA infusion. Following infusion, monitor for thrombocytopenia as well as other signs and symptoms of TMA. Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage if clinically indicated.

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.

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

Gene Therapy for Spinal Muscular Atrophy: Safety and Early Outcomes

Waldrop MA, Karingada C, Storey MA, et al.
Pediatrics. 2020;146(3):e20200729.

A retrospective review that reports the safety and early efficacy of ZOLGENSMA (onasemnogene abeparvovec-xioi) in patients with spinal muscular atrophy aged <2 years treated in the state of Ohio.[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 spinal muscular atrophy (SMA).[2-4]

Indication and Important Safety Information

Indication

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Study methods

Study design[1]

A retrospective review of the key safety and early outcome data of a one-time gene therapy in 21 patients with SMA aged 1-23 months.

- Patients were included from 4 children's hospitals in Ohio
- Patients were either presymptomatic and discovered after confirmation of a positive newborn screen result (n=5), or genetically confirmed and symptomatic without end-stage disease (n=16)
- All patients received ZOLGENSMA® (onasemnogene abeparvovec-xioi) and completed their prednisolone course and taper by April 30, 2020
- Patients initiated 1 mg/kg prednisolone 1 day prior to receiving ZOLGENSMA
- Follow-up laboratory studies were obtained weekly for at least 4 weeks post treatment, including platelets, aspartate aminotransferase (AST), alanine aminotransferase (ALT), γ-glutamyl transpeptidase (GGT), prothrombin, bilirubin, and troponin-I
  - If at any point the AST, ALT, or GGT increased to >2 times normal, the prednisolone dose was increased to 2 mg/kg per day

Outcome measures[1]

Motor function as measured by Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)*

Motor milestone achievement as assessed by ability to sit

Oral feeding

Respiratory status as assessed by bilevel positive airway pressure (BiPAP) use

Safety as measured by laboratory values, including AST, ALT, and GGT

*Because of the retrospective and multisite nature of this review, 6/21 patients were not assessed by CHOP INTEND.

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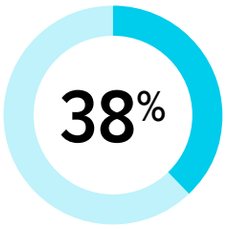
Study design

Considerations[1]

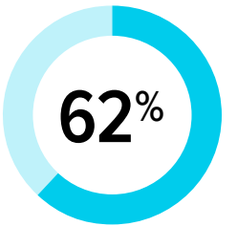
- Patients who previously received nusinersen (n=11) were required to wait 3 months after last dose before receiving gene therapy
  - One patient received gene therapy 1 month after a nusinersen dose, an antisense oligonucleotide with known potential to lower platelets, and was noted to have a concurrent parainfluenza 3 infection
  - Subsequent candidates were required to wait 3 months after last nusinersen dose before receiving gene therapy
- Patients could not be ill at the time of gene therapy. If a patient had been ill, at least 9 days were required from resolution of illness before dosing, and normal laboratory values obtained

Key patient characteristics[1]

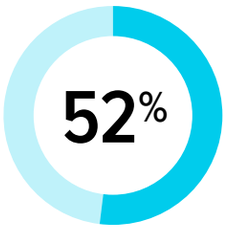
- **Weight range at infusion:** 4.2 kg – 11.7 kg
- **Mean age (range) at infusion:** 10 (1-23) months



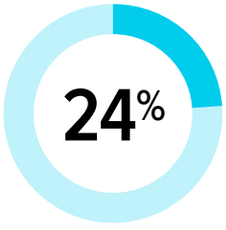
(8/21) of patients were **<6 months of age** at dosing



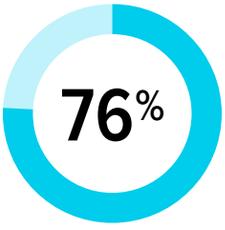
(13/21) of patients were **≥6 months of age** at dosing



(11/21) of patients had **previously received nusinersen**



(5/21) of patients were **presymptomatic**



(16/21) of patients were **symptomatic without end-stage disease**

Important Safety Information

WARNINGS AND PRECAUTIONS

Elevated Troponin-I

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ADVERSE REACTIONS

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

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Results

Summary of functional data in all treated children[1]

Patient	CHOP Baseline, Unless Specified	CHOP 1 mo After	CHOP 2 mo After	CHOP 3 mo After	CHOP 4 mo After	Sitting Before?	Sitting After?	Oral Feeding Before?	Oral Feeding After?	BiPAP Before?	BiPAP After?
1[a]	—	—	—	—	—	N/A	Yes	Yes	Yes	No	No
2[a]	51	—	56	—	—	N/A	Yes	Yes	Yes	No	No
3[a]	62	64	—	—	—	N/A	Yes	Yes	Yes	No	No
4	25	29	29	—	—	N/A	No	Yes	Yes	No	No
5	22	—	—	—	26	N/A	No	No	No	Yes	Yes
6	28	28	35	48	—	N/A	Yes	No	Yes, partial	Yes, night	No
7	25	—	—	25	—	N/A	No	Yes	No	No	Yes, vent
8[a]	62	—	64	—	—	N/A	Yes	Yes	Yes	No	No
9[a]	24 Bayley	—	33 Bayley	—	—	Yes	Yes	Yes	Yes	No	No
10	26	34	—	38	—	No	Yes	No	Yes, partial	Yes, night	Yes, intermittent
11	51	62	59	—	—	No	Yes	Yes, partial	Yes, partial	Yes, intermittent	Yes, intermittent
12	36 HINE, 6 AIMS	—	35	—	—	No	No	Yes	Yes	Yes, night	Yes, night
13	44	47	49	—	—	Yes	Yes	Yes	Yes	No	No
14	38	47	48	—	—	No	No	No	No	Yes, night	Yes, night
15	28 Bayley	28 Bayley	28 Bayley	28 Bayley	—	Yes	Yes	Yes	Yes	No	No
16	34	42	—	—	—	No	No	Yes, partial	Yes, partial	Yes, night	Yes, night
17	43	—	46	—	—	Yes	Yes	—	—	—	—
18	15 HFMSE	15 HFMSE	16 HFMSE	—	—	Yes	Yes	Yes, partial	Yes, partial	No	No
19	49	51	49	50	—	No	No	Yes	Yes	Yes, night	Yes, night
20	52	52	52	54	—	Yes	Yes	Yes, partial	Yes, partial	Yes, night	Yes, night
21	9 RHS	15 RHS	15 RHS	18 RHS	—	Yes	Yes	Yes	Yes	No	No

Note: Some children did not have the Children's Hospital of Philadelphia (CHOP) Infant Test of Neuromuscular Disorders completed, and for those children, the outcome measure used is listed. Because of the retrospective and multisite nature of this review, this was unavoidable, and outcome measures are listed as obtained. AIMS, Alberta Infant Motor Scale; Bayley, Bayley Scales of Infant and Toddler Development, 3rd Edition, Gross Motor Subtest raw score; HFMSE, Hammersmith Functional Motor Score Expanded; HINE, Hammersmith Infant Neurological Examination; N/A, not applicable; RHS, Revised Hammersmith Score; —, value not obtained.

[a]Denotes those identified from newborn screening.

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

Results (cont'd)

Oral feeding[1]

94% (16/17) of patients who were feeding orally before treatment maintained this ability after treatment.[a,b]

- All 4 patients who were partially orally feeding before gene therapy have continued to make progress; however, none were exclusively feeding orally

2 patients dosed at 4.5 and 8 months of age were unable to feed orally prior to gene therapy, but are now able to eat some purees.

[a]8/16 patients who maintained ability to feed orally after treatment were previously treated with another disease-modifying therapy.

[b]One patient dosed at 5 months of age was symptomatic before treatment and developed a significant respiratory illness 2 weeks after gene therapy, requiring subsequent tracheostomy and gastric feeding tube.

Respiratory support[1]

91% (10/11) of patients who were independent of BiPAP support before gene therapy maintained independence after treatment.[c]

- 8 patients were on BiPAP before gene therapy, and 7 remain on BiPAP after treatment
- 1 patient has transitioned to intermittent use only when ill or after a particularly tiring day
- 1 patient no longer requires BiPAP

[c]3/10 patients who maintained independence from BiPAP support after treatment were previously treated with another disease-modifying therapy.

Motor milestones[1]

Patients aged ≥6 months at infusion:

- 7/7 patients who were sitting before gene therapy maintained this milestone[d]
- 2/6 patients who were not sitting before gene therapy were able to sit after gene therapy

Patients aged <6 months at infusion:

- 5/8 patients were sitting after gene therapy[e]

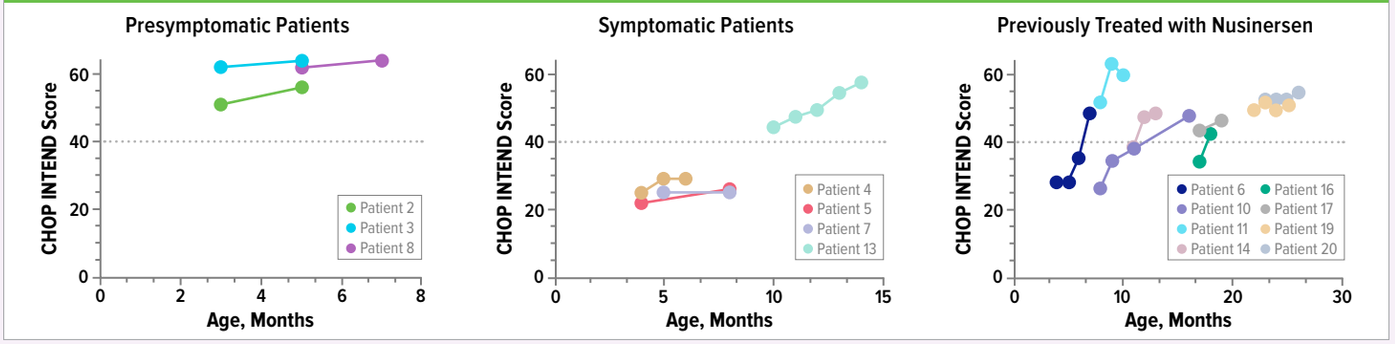
[d]5/7 patients who maintained the ability to sit independently were previously treated with another disease-modifying therapy.

[e]Out of 8 patients who were sitting after gene therapy, 1 patient was previously treated with another disease-modifying therapy.

Motor function[1]

89% (17/19) of patients who completed at least 2 functional assessments had objective improvements of ≥1 point on functional outcome scores by 4 months after gene therapy.[f]

CHOP INTEND SCORES[g]



[f]11/17 patients who had objective improvements of ≥1 point on functional outcome scores by 4 months after treatment were previously treated with another disease-modifying therapy.

[g]Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) values over time if available (baseline to a few months after gene therapy). On the left, children who were identified and treated before symptoms are represented. CHOP INTEND was not completed for patients 1 and 9, so there are no data for them. In the middle, symptomatic children who were treatment naive before gene therapy are represented. CHOP INTEND was not completed on patients 12 and 15, so there are no data for them. On the right, children who transitioned from nusinersen to onasemnogene abeparvovec-xioi are represented. CHOP INTEND was not completed for patients 9, 18, and 21. Dashed line at 40 denotes level that is not reached in children with untreated SMA Type 1.

Important Safety Information

WARNINGS AND PRECAUTIONS

Thrombocytopenia

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were typically observed within the first two weeks after ZOLGENSMA infusion. Monitor platelet counts before ZOLGENSMA infusion and on a regular basis for at least 3 months afterwards.

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Summary of important clinical and safety data in all treated children[1]

Patient	Age at Infusion, mo	Wt at Infusion, kg	*SMN2* Copy No.	Nusinersen Previously?	Platelets Day 7	AST Peak (nl <60)	ALT Peak (nl <50)	GGT Peak (nl <78)	Fever on Day 3-4	No. Weeks on "Full Steroid Dose"
1[a]	1	4.2	2	No	154	62	36	—	No	4
2[a]	2	5.4	3	No	—	53	53	20	No	6
3[a]	3	4.8	3	No	186	92	79	38	No	4
4	4	6.5	2	No	179	124	67	23	Yes	4
5	4	5.1	2	No	234	507	469	201	Yes	11
6	4.5	5.9	2	Yes	384	53	40	20	No	6
7	5	6.5	2	No	297	129	96	58	No	4
8[a]	5	9.2	4	No	204	144	89	13	No	4
9[a]	6	8.8	4	Yes	219	172	192	62	Yes	11
10	8	7.5	2	Yes	33	339	228	111	Yes	10.5
11	8	7.9	2	Yes	65	122	62	17	Yes	4
12	8	8.1	2	No	171	807	1187	251	No	14
13	10	9.7	3	No	146	118	113	21	Yes	6
14	11	10	2	Yes	129	83	54	18	No	4
15	12	8.2	3	No	559[b]	1471	1794	163	Yes	10
16	17	11	2	Yes	108	116	108	26	Yes	4
17	17	8.2	3	Yes	142	177	212	13	No	8
18	19	12	3	Yes	127	1040	1137	83	Yes	10
19	22	8.0	3	Yes	110	1953	1935	376	No	13.5
20	23	10.9	2	Yes	182	66	47	15	No	7
21	23	11.7	2	Yes	52	1114	1002	240	No	11

—, not applicable.

[a]Denotes those identified via newborn screening.

[b]Denotes the child who did not have a decline in platelets. Patient 1 did not have GGT checked. Patient 2 was not able to obtain laboratories on day 7.

Adverse events[1]

In 7 of 9 patients who were ≤6 months of age at infusion, there was no significant elevation in AST, ALT, or GGT. Gene therapy was well tolerated.

In older and heavier patients, the liver impact was greater, though all patients remained clinically well and without signs of liver dysfunction.

- 67% (8/12) of patients ≥8 months of age at infusion had elevations of ≥2 times the upper limit of normal in AST and/or ALT
- 83% (10/12) of patients who were ≥8 kg at infusion had elevations of ≥2 times the upper limit of normal in AST and/or ALT

In 90% (19/21) of patients, a transient decline in platelet count was observed 1 week post-treatment, regardless of age or weight.

- By day 14, all platelet counts had returned to normal

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Conclusions

Authors' conclusions[1]

All symptomatic patients experienced subjective and objective functional improvements in motor function. In the 5 patients treated presymptomatically, no signs of weakness characteristic of SMA have developed over follow-up periods of 2-8 months. Parents have consistently reported improvements in motor skills for patients, while objective testing by physical therapists have shown 89% of patients have had improvements in their outcome measures.

ZOLGENSMA was well tolerated in all patients. To help minimize adverse events, the authors suggest adhering to the following recommendations:

- Complete a thorough screening process prior to treatment
- Practice social isolation to minimize the risk of illness post-treatment
- Monitor patients closely post-treatment
- Delay gene therapy if patients are ill
- Delay live vaccinations until 4 weeks after the prednisolone course and taper have been completed

Regular testing and monitoring are recommended until the prednisolone course has been completed.

- A successful post–gene therapy clinical course is dependent on prednisolone administration
- Just over half of the patients in the study required a prolonged prednisolone course
- All immune responses were controlled with prednisolone alone and did not require more aggressive immune suppression, regardless of patient age or weight at dosing
- Nearly all patients had a drop in platelet count on day 7 following gene therapy. This is likely complement mediated, given the timing

Important Safety Information

WARNINGS AND PRECAUTIONS

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Study summary

- In patients 6 months or younger, gene therapy was well tolerated
  - In this young group, serum transaminase (AST and ALT) elevations were modest and not associated with GGT elevations
- Initial prednisolone administration matched that given in the clinical trials
  - In older patients, elevations in AST, ALT, and GGT were more common and required a higher dose of prednisolone, but all were without clinical symptoms
- Nineteen of 21 (90%) patients experienced an asymptomatic drop in platelets in the first week after treatment that recovered without intervention
- Of the 19 patients with repeated outcome assessments, 11% (n=2) experienced stabilization and 89% (n=17) experienced improvement in motor function

All symptomatic patients experienced subjective and objective improvements in motor function[1]

In presymptomatic patients, no signs of weakness characteristic of SMA have developed over follow-up periods of 2-8 months.

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

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References: 1. Waldrop MA, Karingada C, Storey MA, et al. Gene therapy for spinal muscular atrophy: safety and early outcomes. *Pediatrics*. 2020;146(3):e20200729. **2.** ZOLGENSMA [prescribing information]. Bannockburn, IL: Novartis Gene Therapies, Inc; 2021. **3.** Al-Zaidy SA, Kolb SJ, Lowes L, et al. AVXS-101 (onasemnogene abeparvovec) for SMA1: comparative study with a prospective natural history cohort. *J Neuromuscul Dis.* 2019;6(3):307-317. **4.** FDA approves innovative gene therapy to treat pediatric patients with spinal muscular atrophy, a rare disease and leading genetic cause of infant mortality [press release]. Bethesda, MD: US Food and Drug Administration; May 24, 2019. Accessed July 21, 2020.

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