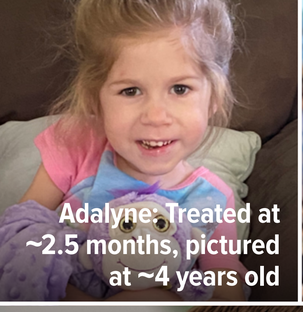
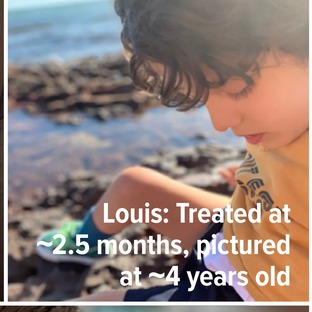
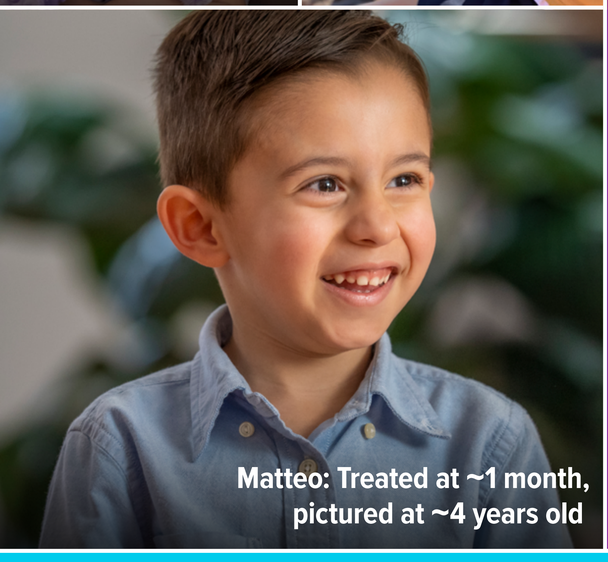

Adalyne: Treated at ~2.5 months, pictured at ~4 years old


Louis: Treated at ~2.5 months, pictured at ~4 years old


Matteo: Treated at ~1 month, pictured at ~4 years old

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OVER 4 YEARS AGO, THESE CHILDREN WITH SMA TYPE 1 RECEIVED ONE-TIME-ONLY ZOLGENSMA[1,2]

SMA=spinal muscular atrophy

Meet Matteo

AND FOLLOW HIS JOURNEY FROM BIRTH TO OVER 4 YEARS POST TREATMENT

SCROLL DOWN

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: Serious Liver Injury and Acute Liver Failure

Cases of acute liver failure with fatal outcomes have been reported. Acute serious liver injury, acute liver failure, and elevated aminotransferases can also 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. Administer systemic corticosteroid to all patients before and after ZOLGENSMA infusion. Continue to monitor liver function for at least 3 months after infusion, and at other times as clinically indicated. If acute serious liver injury or acute liver failure is suspected, promptly consult a pediatric gastroenterologist or hepatologist.

Please see accompanying Full Prescribing Information, also available at ZOLGENSMA-hcp.com.

DIAGNOSIS

BIRTH

Matteo's before

FROM DIAGNOSIS TO ZOLGENSMA TREATMENT DAY

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At 5 months gestation, doctors suspected Matteo had SMA[1]

Family screening showed that his parents, Nicole and Derwin, were carriers; he was tested in utero. Matteo's SMA Type 1 diagnosis was confirmed when he was born.[1]

Genetic testing revealed[3]:

- Bi-allelic deletion of *SMN1*
- 2 copies of *SMN2*

> ***We decided on this treatment because it was a one-time treatment."*** **– Nicole, mother of Matteo**

Matteo's parents researched available clinical trials. They explored one-time-only gene therapy for their son, as Matteo was diagnosed at a time when there were no FDA-approved treatments for SMA.

Matteo was enrolled in the high-dose cohort of the ZOLGENSMA START trial

The START clinical trial is a completed, open-label, single-arm, dose-escalation clinical trial of symptomatic patients with SMA Type 1 that enrolled a low-dose cohort (n=3) and a high-dose cohort (n=12).[2,3] The primary endpoint was 24-month safety. Secondary endpoints were event-free survival (defined as time until death or the need for permanent ventilatory support consisting of ≥16 hours of respiratory assistance per day continuously for ≥14 days) and change from baseline in CHOP INTEND. Exploratory endpoints were motor milestone and developmental achievements.

For more information about ZOLGENSMA clinical trials, visit **ZOLGENSMA-hcp.com**.

CHOP INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

Important Safety Information

WARNINGS AND PRECAUTIONS

Systemic Immune Response

Patients with underlying active infection, either acute or chronic uncontrolled, could be at an increased risk of serious systemic immune response. Administer ZOLGENSMA to patients who are clinically stable in their overall health status (e.g., hydration and nutritional status, absence of infection). Postpone ZOLGENSMA in patients with infections until the infection has resolved and the patient is clinically stable.

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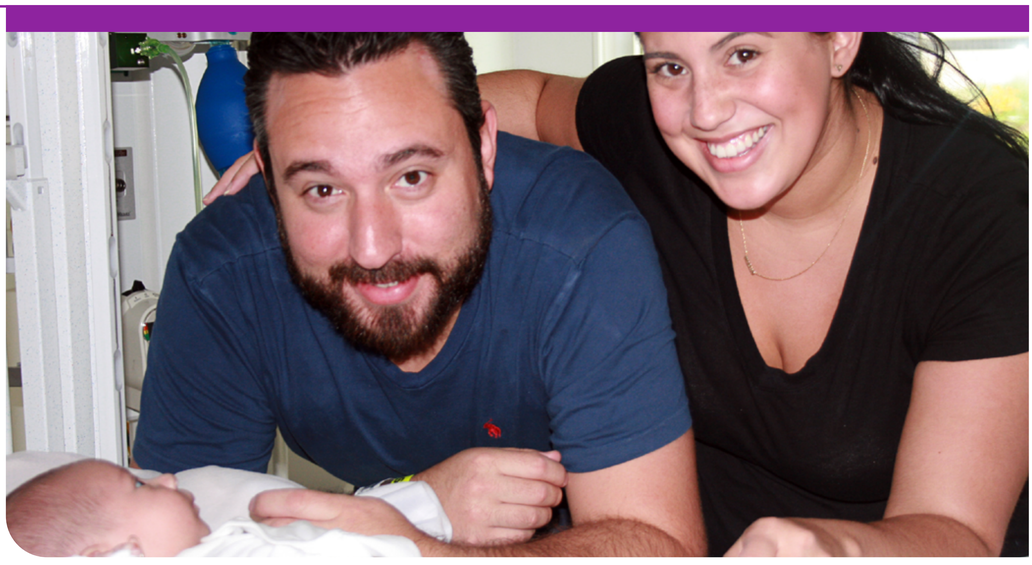
1 DAY BEFORE ZOLGENSMA INFUSION

Matteo started a daily corticosteroid regimen: dosed with 1 mg/kg oral prednisolone[2]

- Per the regimen detailed in the **Full Prescribing Information**, treatment with systemic corticosteroids before and after ZOLGENSMA infusion is required
- Due to increased risk of serious systemic immune response, administer ZOLGENSMA to patients who are clinically stable in their overall baseline health status

TREATMENT DAY



At ~1 month of age, Matteo received his one-time-only ZOLGENSMA infusion[4]

Baseline testing is required for all patients before ZOLGENSMA treatment[2]

- Anti-AAV9 antibody titers ≤1:50
- Liver function,[a] creatinine, complete blood count (including hemoglobin and platelet count), and troponin-I

Matteo's baseline CHOP INTEND score[4]: 50

[a]Clinical exam, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, albumin, prothrombin time, partial thromboplastin time (PTT), and international normalized ratio (INR).

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.

Please see accompanying Full Prescribing Information, also available at ZOLGENSMA-hcp.com.

Matteo's after

FROM 1 MONTH TO MORE THAN 4 YEARS AFTER TREATMENT

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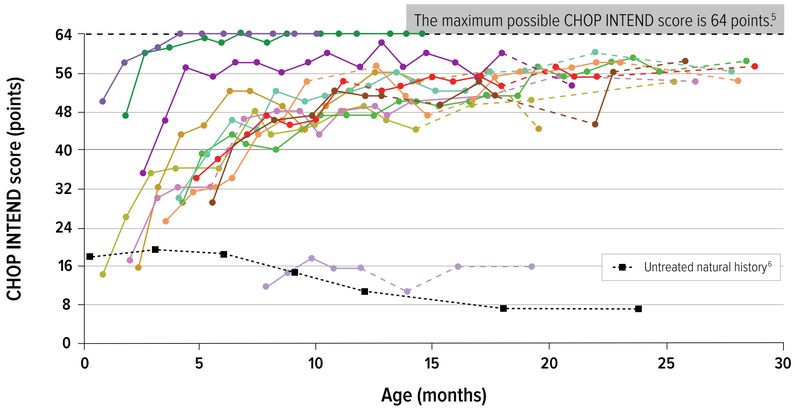
MATTEO TURNED 1

Data from START, a completed 24-month, Phase 1 clinical trial

Matteo maintained improvements in motor function[4]:

- At 1 month post infusion, Matteo's CHOP INTEND score was **58**, 8 points above baseline
- At 3 months post infusion, his score was **64**

CHOP INTEND scores from the START high-dose cohort[4]



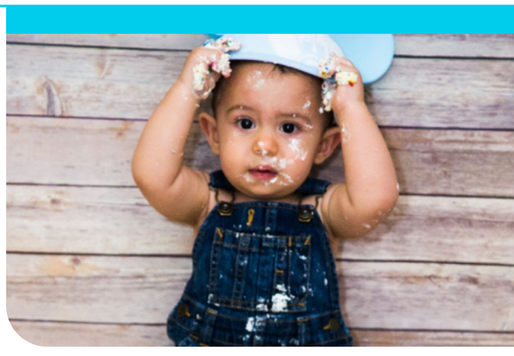
CHOP INTEND score	n (%)
≥40	11 (92%)
≥50	10 (83%)
≥60	2 (17%)

Individual patient data from the high-dose cohort are shown in the CHOP INTEND chart.

Scores on the CHOP INTEND scale of motor function range from 0 to 64, with higher scores indicating better function.[5] The gray line at 40 represents the CHOP INTEND score that children with SMA type 1 would not typically achieve and maintain, according to natural history.[7]

Untreated patients with SMA Type 1 in historical controls did not typically achieve or maintain CHOP INTEND scores of 40 or above[7]

Matteo achieved head control and sitting without support[4]



In the START trial high-dose cohort[2,4]:

- **92% (11/12) of patients** achieved head control
- **75% (9/12) of patients** were able to sit without support for 30 seconds or longer

In natural history, 0% of patients with SMA Type 1 were able to sit unassisted[8]

Important Safety Information

WARNINGS AND PRECAUTIONS

Thrombotic Microangiopathy

Cases of thrombotic microangiopathy (TMA) were reported to occur generally within the first two weeks after ZOLGENSMA infusion. TMA can result in life-threatening or fatal outcomes. Obtain baseline creatinine and complete blood count before ZOLGENSMA infusion. Following infusion, monitor platelet counts closely as well as other signs and symptoms of TMA. Consult a pediatric hematologist and/or pediatric nephrologist immediately to manage as clinically indicated.

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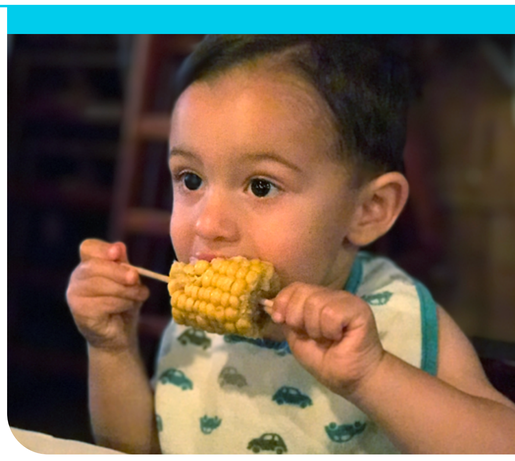
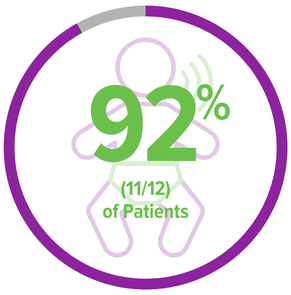
MATTEO TURNED 2

Matteo was able to speak, swallow, and feed orally[4]

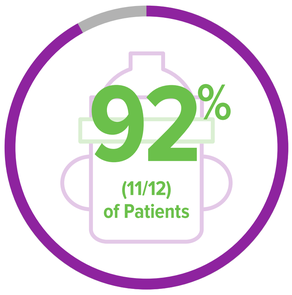
In the START trial high-dose cohort, the majority of patients could speak, swallow, and feed orally by 24 months post ZOLGENSMA infusion.[4,9]



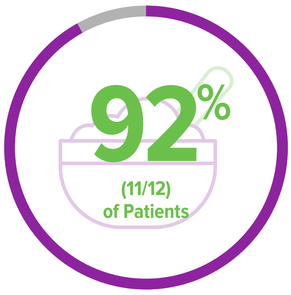
Speaking



Swallowing
(at last assessment)[a]



Feeding Orally
(at last assessment)



[a]Patients were last assessed at 24 months; however, one patient had the last assessment at 12 months.

In natural history, nearly all patients with SMA Type 1 required nutritional support by **12 months of age**[10]

Matteo continued to breathe independently without permanent ventilation[4]

In the START trial high-dose cohort, **100% (12/12) of patients** were alive and free of permanent ventilation at 24 months post treatment.[2,4]

Important Safety Information

WARNINGS AND PRECAUTIONS

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. Consider consultation with a cardiologist if troponin elevations are accompanied by clinical signs or symptoms.

Please see accompanying Full Prescribing Information, also available at ZOLGENSMA-hcp.com.

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MATTEO TURNED 3

Matteo walked without assistance[4]

"Matteo can walk. He can run. He can jump. He can climb up the stairs. He can play in the playground. He can eat. He can talk. He's very vocal."

– Nicole, mother of Matteo

"I think it's important to share our story because it gives people hope. It shows people that the treatment is working [for him]."

– Nicole, mother of Matteo

Important Safety Information

ADVERSE REACTIONS

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

Please see accompanying Full Prescribing Information, also available at ZOLGENSMA-hcp.com.

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MATTEO TURNED 4

Data from START long-term follow-up, an ongoing, 15-year follow-up study of ZOLGENSMA-treated patients from the START clinical trial[11]

More than 4 years post treatment, Matteo has maintained motor milestones he achieved in START[1]

A total of 10 out of 12 high-dose patients enrolled in the long-term follow-up of the START study. As of the December 2019 data cut[1]*:

- **100% (10/10)** of patients were alive and free of permanent ventilation
- **100% (10/10)** of patients have maintained all motor milestones achieved at the end of START
  - 6 out of 10 patients did not receive additional disease-modifying treatments for SMA
- **2 patients** gained the ability to stand with assistance after the end of the START trial
  - Neither patient had received another disease-modifying therapy

*The START long-term follow-up is an ongoing, 15-year follow-up study of ZOLGENSMA-treated patients from the START clinical trial. The **primary endpoint** is long-term safety as assessed by the incidence of serious adverse events and adverse events of special interest.[11]

Patients with SMA Type 1 in historical controls did not typically achieve or maintain motor milestones[8]

CONSIDER ZOLGENSMA

The one-time-only dose to stop SMA progression[2,12]

- The first gene therapy for pediatric patients less than 2 years of age with SMA
- ZOLGENSMA is designed to restore SMN protein expression by replacing the function of the missing *SMN1* gene

Discover more at ZOLGENSMA-hcp.com.

Important Safety Information

WARNINGS AND PRECAUTIONS

Systemic Immune Response

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EFFICACY DEMONSTRATED IN PHASE 3 PIVOTAL TRIAL

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STR1VE

The efficacy of ZOLGENSMA was evaluated in STR1VE, a completed, open-label, single-arm, multicenter, Phase 3 clinical trial of patients with SMA Type 1 (N=22; genetically confirmed bi-allelic *SMN1* deletion, 1-2 copies of *SMN2*, and <6 months of age at symptom onset and treatment)[13]

Survival

91% (20/22) of patients were alive and free of permanent ventilation at the 14-months-of-age study visit, a **primary endpoint**, and at 18 months of age[1,a-c]

Sitting independently

59% (13/22) of patients were sitting without support for ≥30 seconds at the 18-months-of-age study visit, a **primary endpoint**[1,a]

- Patients with SMA Type 1 in historical controls do not typically achieve or maintain motor milestones[8]

Ability to thrive

41% (9/22) of patients met criteria for ability to thrive at 18 months of age, a secondary endpoint[1,d]

Respiratory support

68% (15/22) of patients did not require noninvasive respiratory support at any point during the study[1]

- 4/22 patients required ventilatory support as assessed by Trilogy BiPAP data alone at 18 months of age, a secondary endpoint

Motor function improvements

The mean CHOP INTEND score increased from 32 points (range 18-52) at baseline to **53.5** (range 42-60) at 14 months[1]

- Mean CHOP INTEND scores increased as early as month 1, and scores were maintained or improved through the end of the study

SCROLL DOWN FOR FURTHER CLINICAL TRIAL RESULTS

Important Safety Information

WARNINGS AND PRECAUTIONS

Thrombocytopenia

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EFFICACY DEMONSTRATED IN PHASE 3 PIVOTAL TRIAL (cont'd)

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[a]One patient was initially classified as presymptomatic and removed from the intent-to-treat (ITT) data set included in the Prescribing Information. The patient has been confirmed to be symptomatic at the time of gene therapy and included in the final ITT analysis.[1]

[b]One patient died at 7.8 months from respiratory failure, which was deemed unrelated to treatment. One patient withdrew consent at 11.9 months of age; this patient required permanent ventilation at 11 months of age prior to withdrawal of consent.[1]

[c]One patient discontinued participation at the age of 18.0 months, before the month 18 end-of-study visit, due to an adverse event of respiratory distress deemed unrelated to treatment. Patient was alive and without permanent ventilation at the time of withdrawal.[1]

[d]Ability to thrive was defined as ability to tolerate thin liquids as demonstrated through a formal swallowing test, maintenance of weight (≥3rd percentile for age and gender, as defined by WHO guidelines), and independence from mechanical or non-oral nutritional support.[1]

Results and outcomes vary among children based on several factors, including how far their SMA symptoms had progressed prior to receiving treatment.

To learn more about the ZOLGENSMA clinical trials, go to ZOLGENSMA-hcp.com.

Important Safety Information

WARNINGS AND PRECAUTIONS

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Indication and Important Safety Information

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Important Safety Information (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

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ADVERSE REACTIONS

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

Please see accompanying Full Prescribing Information, also available at ZOLGENSMA-hcp.com.

References: 1. Data on file. AveXis, Inc. 2020. **2.** ZOLGENSMA [prescribing information]. Bannockburn, IL: Novartis Gene Therapies, Inc; 2023. **3.** Novartis Gene Therapies, Inc. Gene transfer clinical trial for spinal muscular atrophy type 1. https://clinicaltrials.gov/ct2/show/NCT02122952. ClinicalTrials.gov identifier: NCT02122952. Updated September 15, 2022. Accessed February 17, 2023. **4.** Data on file. AveXis, Inc. 2019. **5.** Glanzman AM, Mazzone E, Main M, et al. The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord.* 2010;20(3):155-161. **6.** Kolb SJ, Coffey CS, Yankey JW, et al; NeuroNEXT Clinical Trial Network on behalf of the NN101 SMA Biomarker Investigators. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol.* 2017;82(6):883-891. **7.** Lowes LP, Alfano LN, Arnold WD, et al. Impact of age and motor function in a phase 1/2A study of infants with SMA type 1 receiving single-dose gene replacement therapy. *Pediatr Neurol.* 2019;98:39-45. **8.** De Sanctis R, Coratti G, Pasternak A, et al. Developmental milestones in type I spinal muscular atrophy. *Neuromuscul Disord.* 2016;26(11):754-759. **9.** Al-Zaidy S, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatr Pulmonol.* 2019;54(2):179-185. **10.** Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology.* 2014;83(9):810-817. **11.** Novartis Gene Therapies, Inc. Long-term follow-up study for patients from AVXS-101-CL-101 (START). https://clinicaltrials.gov/ct2/show/NCT03421977. ClinicalTrials.gov identifier: NCT03421977. Updated November 22, 2022. Accessed February 17, 2023. **12.** 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. **13.** Novartis Gene Therapies, Inc. Gene replacement therapy clinical trial for patients with spinal muscular atrophy type 1 (STR1VE). https://clinicaltrials.gov/ct2/show/NCT03306277. ClinicalTrials.gov identifier: NCT03306277. Updated August 16, 2022. Accessed February 17, 2023.

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