



## **AveXis receives FDA approval for Zolgensma®, the first and only gene therapy for pediatric patients with spinal muscular atrophy (SMA)**

May 24, 2019

- *SMA is a rare genetic disease that leads to progressive muscle weakness, paralysis and, when left untreated in its most severe form, permanent ventilation or death for most patients by age 2<sup>[1],[2]</sup>*
- *Zolgensma (onasemnogene abeparvovec-xioi) is approved for the treatment of pediatric patients less than 2 years of age with spinal muscular atrophy (SMA) including those who are pre-symptomatic at diagnosis*
- *Zolgensma is designed to address the genetic root cause of SMA by replacing the defective or missing SMN1 gene to halt disease progression with a single, one-time infusion*
- *Data from the Phase 3 STR1VE trial show prolonged event-free survival, increases in motor function and significant milestone achievement in patients with SMA Type 1, consistent with the Phase 1 START trial*
- *In the START trial, patients treated with Zolgensma achieved motor milestones never seen in the natural history of the disease, including sitting, talking and some patients walking, with no waning of effect nearly four years post-dosing*

**Basel, May 24, 2019** - AveXis, a Novartis company, today announced the US Food and Drug Administration (FDA) has approved Zolgensma® (onasemnogene abeparvovec-xioi) 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. Zolgensma is designed to address the genetic root cause of SMA by providing a functional copy of the human SMN gene to halt disease progression through sustained SMN protein expression with a single, one-time intravenous (IV) infusion. Zolgensma is the first and only gene therapy approved by the FDA for the treatment of SMA, including those who are pre-symptomatic at diagnosis.

"A diagnosis of SMA is devastating, leaving untreated babies who have the most severe form with painfully short, highly medicalized lives, during which they are unable to lift their heads, sit or roll, have difficulty swallowing and breathing and need 24-hour care," said Jerry Mendell, M.D., principal investigator at the Center for Gene Therapy at The Abigail Wexner Research Institute of Nationwide Children's Hospital in Columbus, OH. "In the START clinical trial we conducted with Zolgensma, all children were alive at the conclusion of the study and many were able to sit, roll, crawl, play and some could walk. This level of efficacy, delivered as a single, one-time therapy, is truly remarkable and provides a level of unprecedented hope for families battling SMA Type 1. We now have data four years out from the trial, and we see the durability of this gene therapy."

"The approval of Zolgensma is a testament to the transformational impact gene therapies can have in reimagining the treatment of life-threatening genetic diseases like spinal muscular atrophy," said Vas Narasimhan, CEO of Novartis. "We believe Zolgensma could create a lifetime of possibilities for the children and families impacted by this devastating condition."

SMA is a rare, genetic neuromuscular disease caused by a defective or missing *SMN1* gene. Without a functional *SMN1* gene, infants with SMA lose the motor neurons responsible for muscle functions such as breathing, swallowing, speaking and walking.<sup>[1]</sup> Left untreated, muscles become progressively weaker.<sup>[1],[2]</sup> In the most severe form, this eventually leads to paralysis and ultimately permanent ventilation or death by age 2 in more than 90% of cases.<sup>[3]</sup> SMA is the leading cause of genetic infant death.<sup>[4]</sup> Approximately 450 to 500 infants are born with SMA in the US annually.<sup>[5],[6]</sup> It is imperative to diagnose SMA and begin treatment, including proactive supportive care, as early as possible to halt irreversible motor neuron loss and disease progression.<sup>[7]</sup> This is especially critical in the most severe form where degeneration starts shortly before birth and escalates quickly.<sup>[8]</sup> With states adding SMA to their genetic newborn screening panel, babies with SMA can begin to be widely identified at birth and the ability to have earlier intervention can be improved.<sup>[9]</sup>

"Zolgensma's one-time dose of gene therapy has the potential to make a truly transformative impact on this life-threatening disease," said Kenneth Hobby, president of Cure SMA, a patient advocacy organization dedicated to the care, treatment and cure of SMA. "Our organization is leading the way to a world without SMA and we are excited the FDA's approval of Zolgensma brings patients and families a powerful new treatment which corrects the underlying cause of the disease."

The approval of Zolgensma is based on data from the ongoing Phase 3 STR1VE trial and the completed Phase 1 START trial evaluating the efficacy and safety of a one-time IV infusion of Zolgensma in patients with SMA Type 1 who showed symptoms of SMA at <6 months of age, with one or two copies in the STR1VE trial or two copies in the START trial of the *SMN2* backup gene and who have bi-allelic *SMN1* gene deletion or point mutations. These data show Zolgensma provides unprecedented rates of survival never seen in the natural history of the disease; rapid motor function improvement, often within one month of dosing; and, durable milestone achievement, including the ability to sit without support, a milestone never achieved in untreated patients. Safety observations in STR1VE were comparable to those seen in the START trial. The most commonly observed adverse events were elevated aminotransferases and vomiting.

"We are grateful to the tenacious researchers, partners and families who participated in the Zolgensma clinical trials that helped us achieve this incredible milestone," said Dave Lennon, president of AveXis. "We are proud to bring this one-time gene therapy to pediatric patients with SMA and

remain committed to advancing the science behind Zolgensma to transform SMA, as well as other rare genetic diseases."

Zolgensma will be made available in the US and will be marketed by AveXis, a Novartis company. OneGene Program™, AveXis' comprehensive patient support program, provides a dedicated, personalized support team focused on the needs of each family throughout the Zolgensma treatment journey. This includes answering questions about Zolgensma, verifying reimbursement assistance and coordinating financial assistance programs for eligible patients. For more information, caregivers and healthcare professionals can call 1-855-441-GENE (1-855-441-4363).

Outside of the US, Zolgensma has PRIME (PRiority MEDicines) designation in Europe and is being reviewed under Accelerated Assessment Procedure, and also has accelerated Sakigake designation in Japan. In the interim, AveXis has arranged to make the product available for international markets, subject to local laws and regulations, as a part of its paid Managed Access Program via a collaboration with Durbin, a third-party provider. International inquiries regarding availability of Zolgensma outside of the US may be made by contacting Durbin at AveXisMAP@DurbinGlobal.com or +44-20-8869-6506.

AveXis has an exclusive, worldwide license with Nationwide Children's Hospital to both the intravenous and intrathecal delivery of AAV9 gene therapy for the treatment of all types of SMA; has an exclusive, worldwide license from REGENXBIO for any recombinant AAV vector in its intellectual property portfolio for the in vivo gene therapy treatment of SMA in humans; an exclusive, worldwide licensing agreement with Genethon for in vivo delivery of AAV9 vector into the central nervous system for the treatment of SMA; and a non-exclusive, worldwide license agreement with AskBio for the use of its self-complementary DNA technology for the treatment of SMA.

#### **About Zolgensma Clinical Data**

The efficacy of Zolgensma in pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene was evaluated in STRIVE, an open-label, single-arm clinical trial (ongoing), and in START, an open-label, single-arm, ascending-dose clinical trial (completed). Patients experienced onset of clinical symptoms consistent with SMA before 6 months of age. All patients had genetically confirmed bi-allelic *SMN1* gene deletions, two copies of the *SMN2* gene, and absence of the c.859G>C modification in exon 7 of *SMN2* gene (which predicts a milder phenotype). All patients had baseline anti-AAV9 antibody titers of >1:50, measured by ELISA. In both trials, Zolgensma was delivered as a single-dose intravenous infusion.

Efficacy was established on the basis of survival, and achievement of developmental motor milestones such as sitting without support. Survival was defined as time from birth to either death or permanent ventilation. Permanent ventilation was defined as requiring invasive ventilation (tracheostomy), or respiratory assistance for 16 or more hours per day (including noninvasive ventilatory support) continuously for 14 or more days in the absence of an acute reversible illness, excluding perioperative ventilation. Efficacy was also supported by assessments of ventilator use, nutritional support and scores on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND). CHOP-INTEND is an assessment of motor skills in patients with infantile-onset SMA.

The ongoing clinical trial, STRIVE, enrolled 21 patients (10 male and 11 female) with infantile-onset SMA. Before treatment with Zolgensma, none of the 21 patients required non-invasive ventilator (NIV) support, and all patients could exclusively feed orally (i.e., no need for non-oral nutrition). The mean CHOP-INTEND score at baseline was 31.0 (range 18 to 47). All the patients received  $1.1 \times 10^{11}$  vg/kg of Zolgensma. The mean age of the 21 patients at the time of treatment was 3.9 months (range 0.5 to 5.9 months).

As of the March 2019 data cutoff, 19 patients were alive without permanent ventilation (i.e., event-free survival) and were continuing in the trial, while one patient died at age 7.8 months due to disease progression, and one patient withdrew from the study at age 11.9 months. The 19 surviving patients who were continuing in the trial ranged in age from 9.4 to 18.5 months. By the data cutoff, 13 of the 19 patients continuing in the trial reached 14 months of age without permanent ventilation, one of the study's co-primary efficacy endpoints. In addition to survival, assessment of the other co-primary efficacy endpoint found that 10 of the 21 patients (47.6%) achieved the ability to sit without support for  $\geq 30$  seconds between 9.2 and 16.9 months of age (mean age was 12.1 months). Based on the natural history of the disease, patients who met the study entry criteria would not be expected to attain the ability to sit without support, and only approximately 25% of these patients would be expected to survive (i.e., being alive without permanent ventilation) beyond 14 months of age. In addition, 16 of the 19 patients had not required daily NIV use.

Comparison of the results of the ongoing clinical trial to available natural history data of patients with infantile-onset SMA provides primary evidence of the effectiveness of Zolgensma.

The completed clinical trial, START, enrolled 15 patients (6 male and 9 female) with infantile-onset SMA, 3 in a low-dose cohort and 12 in a high-dose cohort. At the time of treatment, the mean age of patients in the low-dose cohort was 6.3 months (range 5.9 to 7.2 months), and 3.4 months (range 0.9 to 7.9 months) in the high-dose cohort. The dosage received by patients in the low-dose cohort was approximately one-third of the dosage received by patients in the high-dose cohort. However, the precise dosages of Zolgensma received by patients in this completed clinical trial are unclear due to a change in the method of measuring Zolgensma concentration, and to decreases in the concentration of stored Zolgensma over time. The retrospectively-estimated dosage range in the high-dose cohort is approximately  $1.1 \times 10^{11}$  to  $1.4 \times 10^{11}$  vg/kg.

By 24 months following Zolgensma infusion, one patient in the low-dose cohort met the endpoint of permanent ventilation; all 12 patients in the high-dose cohort were alive without permanent ventilation. None of the patients in the low-dose cohort were able to sit without support, or to stand or walk; in the high-dose cohort, 9 of the 12 patients (75.0%) were able to sit without support for  $> 30$  seconds, and 2 patients (16.7%) were able to stand and walk without assistance. Comparison of the results of the low-dose cohort to the results of the high-dose cohort shows a dose-response relationship that supports the effectiveness of Zolgensma.

#### **About Zolgensma® (onasemnogene abeparvovec-xioi)**

Zolgensma (onasemnogene abeparvovec-xioi) is a proprietary gene therapy approved by the US Food and Drug Administration 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. Zolgensma is designed to address the genetic root cause of SMA by providing a functional copy of the human SMN gene to halt disease progression through sustained SMN protein expression with a single, one-time intravenous (IV) infusion. Zolgensma represents the first approved therapeutic in a proprietary platform to treat rare, monogenic diseases using gene therapy. The therapy is also under regulatory review and anticipated to receive approval in Japan and the European Union later this year.

#### **About Spinal Muscular Atrophy (SMA)**

SMA is a severe neuromuscular disease characterized by the loss of motor neurons leading to progressive muscle weakness and paralysis. SMA is

caused by a genetic defect in the *SMN1* gene that codes SMN, a protein necessary for survival of motor neurons.<sup>[1],[2]</sup> The incidence of SMA is approximately 1 in 10,000 live births and it is the leading genetic cause of infant mortality.<sup>[2],[4]</sup> The most severe form of SMA is Type 1, a lethal genetic disorder characterized by rapid motor neuron loss and associated muscle deterioration, resulting in mortality or the need for permanent ventilation support by 24 months of age for more than 90 percent of patients if left untreated.<sup>[3]</sup>

#### **Indication**

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

#### **Limitation of Use:**

The safety and effectiveness of repeat administration of Zolgensma have not been evaluated.

The use of Zolgensma in patients with advanced SMA (e.g., complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

#### **Important Safety Information**

##### **Acute Serious Liver Injury**

**Acute serious liver injury and elevated aminotransferases can occur with Zolgensma. Patients with pre-existing 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 and alanine aminotransferase], total bilirubin and prothrombin time). Administer systemic corticosteroid to all patients before and after Zolgensma infusion. Continue to monitor liver function for at least 3 months after infusion.**

##### **Thrombocytopenia**

Transient decreases in platelet counts, some of which met the criteria for thrombocytopenia, were observed at different time points after Zolgensma infusion. Monitor platelet counts before Zolgensma infusion and on a regular basis afterwards.

##### **Elevated Troponin-I**

Transient increases in cardiac troponin-I levels (up to 0.176 mcg/L) were observed following Zolgensma infusion in clinical trials. The clinical importance of these findings is not known. However, cardiac toxicity was observed in animal studies. 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  $\geq$ 5%) were elevated aminotransferases and vomiting.

Please read full [Prescribing Information](#) for Zolgensma, including Boxed Warning for Acute Serious Liver Injury.

#### **Disclaimer**

This press release contains forward-looking statements within the meaning of the United States Private Securities Litigation Reform Act of 1995. Forward-looking statements can generally be identified by words such as "designed to," "to halt," "hope," "can," "could," "possibilities," "potential," "leading," "excited," "milestone," "committed," "will," "PRIME (Priority Medicines) designation," "Accelerated Assessment Procedure," "accelerated Sakigake designation," "anticipated," "plans," or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for Zolgensma and for the investigational products described in this press release, or regarding potential future revenues from such products. You should not place undue reliance on these statements. Such forward-looking statements are based on our current beliefs and expectations regarding future events, and are subject to significant known and unknown risks and uncertainties. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those set forth in the forward-looking statements. There can be no guarantee that Zolgensma and the investigational products described in this press release will be submitted or approved for sale or for any additional indications or labeling in any market, or at any particular time. Nor can there be any guarantee that such products will be commercially successful in the future. In particular, our expectations regarding such products could be affected by, among other things, the uncertainties inherent in research and development, including clinical trial results and additional analysis of existing clinical data; regulatory actions or delays or government regulation generally; global trends toward health care cost containment, including government, payor and general public pricing and reimbursement pressures and requirements for increased pricing transparency; our ability to obtain or maintain proprietary intellectual property protection; the particular prescribing preferences of physicians and patients; general political and economic conditions; safety, quality or manufacturing issues; potential or actual data security and data privacy breaches, or disruptions of our information technology systems, and other risks and factors referred to in Novartis AG's current Form 20-F on file with the US Securities and Exchange Commission. Novartis is providing the information in this press release as of this date and does not undertake any obligation to update any forward-looking statements contained in this press release as a result of new information, future events or otherwise.

#### **About AveXis**

AveXis, a Novartis company, is dedicated to developing and commercializing novel treatments for patients suffering from rare and life-threatening neurological genetic diseases. Our initial product, Zolgensma, is a proprietary gene therapy approved by the US Food and Drug Administration for the treatment of pediatric patients with SMA less than 2 years of age with spinal muscular atrophy (SMA) with bi-allelic mutations in the survival motor neuron 1 (*SMN1*) gene. In addition to developing Zolgensma to treat all forms of SMA, AveXis also plans to develop other novel treatments for rare neurological diseases, including Rett syndrome and a genetic form of amyotrophic lateral sclerosis caused by mutations in the superoxide dismutase 1 (*SOD1*) gene. For additional information, please visit [www.avexis.com](http://www.avexis.com).

#### **About Novartis**

Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach more than 750 million people globally and we are finding innovative ways to expand access to our latest treatments. About 105 000 people of more than 140 nationalities work at Novartis around the world. Find out more at [www.novartis.com](http://www.novartis.com).

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