AveXis presented robust data at AAN demonstrating efficacy of Zolgensma® in broad spectrum of spinal muscular atrophy (SMA) patients

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- Interim data reported for the first time from STRONG in SMA Type 2 showed rapid motor function gains and milestone achievements with intrathecal Zolgensma (onasemnogene abeparvovec-xioi; AVXS-101)

- New interim data from STR1VE in SMA Type 1 continued to show prolonged event-free survival, increases in motor function and significant milestone achievement consistent with Phase 1 START trial

- Interim data reported for the first time from SPR1NT in pre-symptomatic SMA showed age-appropriate motor milestone achievement

BASEL, Switzerland, May 5, 2019 /PRNewswire/ -- AveXis, a Novartis company, today announced interim data from ongoing trials of the investigational product Zolgensma® (onasemnogene abeparvovec-xioi; AVXS-101)[1] that showed positive results across a broad spectrum of patients with spinal muscular atrophy (SMA). These included the first presentation of data from the Phase 1 STRONG trial, which showed motor function gains and milestone achievements in patients with SMA Type 2 via intrathecal (IT) delivery; new data from the Phase 3 STR1VE trial, which continued to show prolonged event-free survival, increases in motor function and significant milestone achievement consistent with the Phase 1 START trial; and the first presentation of data from the Phase 3 SPR1NT trial, which showed motor milestone achievement consistent with normal development in SMA patients treated pre-symptomatically. These data were presented during the 2019 American Academy of Neurology (AAN) Annual Meeting.

"With just a single, one-time dose, we are seeing Zolgensma provide prolonged survival, rapid motor function improvement and milestone achievements that patients never experience if their disease is left untreated," said David Lennon, President of AveXis. "These robust data presented at AAN represent a growing body of evidence that support the use of Zolgensma as a potential foundational therapy for the treatment of SMA across a variety of populations."

Phase 1 STRONG Data as of March 8, 2019
STRONG is a Phase 1, open-label, dose-comparison, multi-center trial designed to evaluate the safety and tolerability of one-time IT administration of Zolgensma in patients with SMA Type 2 who have three copies of the *SMN2* gene, and who are able to sit but cannot stand or walk at the time of study entry. Patients were stratified into two groups based on age at time of dosing: patients who are ≥6 months but <24 months, and patients who are ≥24 months but <60 months. The primary efficacy outcome for patients who were ≥6 to <24 months is the ability to stand without support ≥3 seconds; the primary efficacy outcome for patients who were ≥24 to >60 months is change in Hammersmith Functional Motor Scale-Expanded (HFMSE) score from baseline. Three dosing strengths are being evaluated. Only 3/34 (8.8 percent) patients were excluded due to elevated AAV9 antibodies.

Patients in the STRONG study showed improvement in motor function, with 19 patients (12/12 dosed at ≥24 to <60 months and 7 who were dosed at ≥6 to <24 months who then became old enough to be evaluated on the HSMSE) having a mean 4.2-point increase from baseline in HFMSE as of their most recent study visit (5-12 months post-treatment). Half of the patients (6/12) who were ≥24 months at dosing experienced a ≥3-point improvement from baseline in HFMSE by one-month post dosing.

Since dosing, 22 motor milestones in 10 patients have been achieved according to the Bayley-III Gross Motor Milestone Scale across the Dose A and Dose B treatment groups, including two patients who gained the ability to stand independently, one of whom went on to walk alone in the younger group, and one additional patient who gained the ability to walk with assistance in the older group. The median duration of follow-up was 6.5 months. Efficacy data from Dose C are not presented because enrollment is not complete.

All patients (n=30) were alive. There were two serious treatment-related adverse events. Both were of transaminase elevation. The frequency of patients with adverse events of transaminase elevation appeared to be lower than that seen with intravenous (IV) administration of Zolgensma.

"With an average of just over six months of data available for these Type 2 patients following treatment with Zolgensma, we are pleased to see they are achieving motor milestones, including the ability to stand and walk," said Olga Santiago, M.D., Chief Medical Officer of AveXis. "Based on these early promising data, we plan to approach regulators to define the path to registration for intrathecal administration of Zolgensma."

Phase 3 STR1VE Data as of March 8, 2019
STR1VE is an ongoing, open-label, single-arm, single-dose, multi-center trial in the U.S. designed to evaluate the efficacy and safety of a one-time IV infusion of Zolgensma in patients with SMA Type 1 who are <6 months of age at the time of gene therapy, with one or two copies of the *SMN2* backup gene and who have bi-allelic *SMN1* gene deletion or point mutations.

As of March 8, 2019, of the 20 patients who could have reached 10.5 months of age or discontinued the study prior to 10.5 months of age, 19 (95 percent) survived without permanent ventilation. Of the 15 patients who could have reached 13.6 months of age or discontinued the study prior to 13.6 months of age, 13 (87 percent) survived without permanent ventilation. Untreated natural history indicates that only 50 and 25 percent of babies with SMA Type 1 will survive event-free by the time they reach 10.5 months of age and 13.6 months of age, respectively. The median age was 14.4 months. As previously disclosed, one patient died from respiratory failure, which was deemed by the investigator and independent Data Safety Monitoring Board to be unrelated to treatment. This patient had demonstrated significant motor improvement prior to the event, with a 27-point increase in CHOP-INTEND from baseline five months post-infusion.

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores increased by an average of 6.9 points one month,

11.7 points three months and 14.3 points five months after gene transfer, reflecting improvement in motor function from baseline. Twenty-one of 22 (95 percent) patients achieved a CHOP-INTEND score of ≥40.

Patients treated with Zolgensma continued to gain motor milestones, including one patient who could crawl, one patient who could pull to a stand and 11 patients who could sit without support for at least 30 seconds according to Bayley-III Gross Motor criteria, an achievement babies with SMA Type 1 never reach in natural history. The 11 patients (50%) achieved the ability to sit without support at a mean age of 11.9 months and at a mean 8.2 months post treatment.

Safety observations in STR1VE are comparable to those seen in the Phase 1 START trial. Adverse events observed include elevated transaminases, platelet count decrease and thrombocytopenia.

These interim data from the multicenter, Phase 3 STR1VE trial are consistent with the findings in the Phase 1 START trial and on track to confirm those results.

Phase 3 SPR1NT Data as of March 8, 2019
SPR1NT is a Phase 3, open-label, single-arm, multi-center trial designed to evaluate the safety and efficacy of a one-time IV infusion of Zolgensma in pre-symptomatic patients with SMA and two or three copies of *SMN2* who are ≤6 weeks of age. The primary outcome measure for patients with two copies of *SMN2* is independent sitting for ≥30 seconds by 18 months. The primary outcome measure for patients with three copies of *SMN2* is standing without support for at least three seconds by 24 months.

As of March 8, 2019, all patients (18/18)* were alive and event-free. Among patients with two copies of *SMN2* (n=8), a mean 8.9-point improvement from baseline in CHOP-INTEND was achieved one-month post dosing, and a mean score of 8.4 points in Bayley-III Gross Motor was achieved by month two. All patients in this group achieved or maintained a CHOP-INTEND score of 50 points, with six patients achieving a score of 60 points and three patients achieving the maximum score of 64.

Patients with two copies of *SMN2* reached age-appropriate motor milestones, including four patients who could sit without support for at least 30 seconds according to Bayley-III Gross Motor criteria, and one patient who could stand with assistance for ≥2 seconds. Untreated natural history indicates that patients with two copies of *SMN2* will never sit without assistance. The median duration of follow-up is 5.4 months and the median age is 6.1 months.

Serious adverse events were cases of croup (n=1), lethargy (n=1), and hypercalcemia (n=1), all of which resolved and were considered unrelated to treatment by investigators. Other observed adverse events included elevated transaminases, elevated blood creatine phosphokinase MB and elevated troponin.

"SMA is rapidly progressive, and we know that intervening as early as possible in the disease course is critical to rescue motor neurons and preserve motor function," said Santiago. "Patients treated with Zolgensma before the onset of symptoms are achieving age-appropriate motor milestones in line with normal development. These SPR1NT data reinforce the potential Zolgensma has as a foundational treatment for patients with SMA."

***One patient was enrolled in to SPR1NT with four copies of SMN2 and was assessed for safety but not efficacy as this patient did not meet the intent-to-treat criteria.*

About Zolgensma®
Zolgensma® (onasemnogene abeparvovec-xioi; AVXS-101) is an investigational gene therapy currently in development as a one-time infusion for SMA Type 1. Zolgensma is designed to address the genetic root cause of SMA and prevent further muscle degeneration by providing a functional copy of the human SMN gene to halt disease progression through sustained SMN protein expression. Zolgensma represents the first in a proprietary platform to treat rare, monogenic diseases using gene therapy. Zolgensma was developed in partnership with Genethon. In December 2018, the FDA accepted the company's Biologics License Application for use of Zolgensma with SMA Type 1 patients. The drug previously received Breakthrough Therapy designation and has been granted Priority Review by the FDA, with regulatory action anticipated in May 2019. In addition, the drug is 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. The incidence of SMA is approximately one in 10,000 live births and is the leading genetic cause of infant mortality. The most severe form of SMA is Type 1, a lethal genetic disorder characterized by rapid motor neuron loss and associated muscle deterioration, which results in mortality or the need for permanent ventilation support by 24 months of age for more than 90 percent of patients.

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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 candidate, Zolgensma, is a proprietary gene therapy currently in development for the treatment of spinal muscular atrophy, or SMA. In addition to developing Zolgensma to treat 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.

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.

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References	
1.	The brand name Zolgensma® (onasemnogene abeparvovec- xioi) has been provisionally approved by the FDA for the investigational product AVXS-101, but the product itself has not received marketing authorization or BLA approval from any regulatory authorities.

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