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AveXis presents new data at EPNS continuing to show significant therapeutic benefit of Zolgensma® in prolonging event-free survival now up to 5 years of age in patients with spinal muscular atrophy (SMA) Type 1

- *New interim data from SPR1NT study supports critical importance of early intervention in pre-symptomatic SMA patients, leading to age-appropriate major milestone gain*
- *Updated results from global STR1VE study demonstrate that Zolgensma® (onasemnogene abeparvovec-xioi) has significant therapeutic benefit in prolonging event-free survival in SMA Type 1 patients versus natural history*
- *Patients in START long-term follow-up study (cohort 2), who are an average age of 4.2 years (oldest patient is 5 years), continue to achieve developmental milestones*

Basel, September 19, 2019 – AveXis, a Novartis company, today announced that new interim data from the Phase 3 SPR1NT trial in pre-symptomatic patients as well as interim data from the ongoing Phase 3 STR1VE clinical program for Zolgensma® (onasemnogene abeparvovec-xioi) showed positive outcomes, demonstrating age-appropriate major milestone gain with pre-symptomatic treatment and prolonged event-free survival* in patients with SMA Type 1. An additional oral presentation highlighted interim results from the long-term follow-up of the Phase 1 START study. These data will be presented during the 2019 European Paediatric Neurology Society (EPNS) Congress.

"For families who never expected their children to reach meaningful motor milestones, the results we're presenting at EPNS demonstrate the life-changing impact Zolgensma can have on children with SMA Type 1," said Olga Santiago, M.D., Chief Medical Officer, AveXis. "It is critical to diagnose SMA and begin treatment as early as possible in order to stop irreversible motor neuron loss and make the achievement of major motor milestones such as crawling, sitting and walking a possibility."

SMA is a rare and devastating genetic disease that leads to progressive muscle weakness, paralysis and, when left untreated in its most severe form (Type 1), death. The disease affects 550-600 infants in Europe.[1,2]

SPR1NT

Phase 3 SPR1NT Data as of May 31, 2019
SPR1NT is an ongoing Phase 3, open-label, single-arm, multi-center trial designed to evaluate the safety and efficacy of a one-time intravenous (IV) infusion of Zolgensma in pre-

symptomatic patients with SMA and two or three copies of *SMN2* who are <=6 weeks of age. As of May 31, 10 patients with two copies of *SMN2*, 12 patients with three copies of *SMN2* and one patient with four copies of *SMN2* were treated. The mean age of patients in the two-copy cohort was 6.6 months at last follow up and 4.6 months for the three-copy cohort. Of the two- and three-copy patients who had completed their six-month swallow evaluation, all had normal swallow function and were fed exclusively by mouth; of the 22 patients being

evaluated overall, all were alive and free of permanent ventilation. All patients with two copies of *SMN2* achieved or maintained a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score of greater than 50, with seven patients achieving a CHOP-INTEND score of greater than or equal to 60 and five patients reaching the maximum score of 64. Of patients with two copies of *SMN2*, six (60%) were able to sit without support for at least 30 seconds at an average age of 7.6 months. Three of these patients (30%) were able to stand with assistance at an average age of 10.1 months. The natural history of untreated patients with SMA indicates that patients with two copies of SMN2 will never sit without assistance.[3]

Thirteen of the 18 patients (72.2%) experienced at least one treatment-emergent adverse event (TEAE) and seven (38.9%) were reported to have a TEAE considered by the investigator to be related to Zolgensma. Three serious TEAEs were reported in three treated patients: croup (one patient), lethargy (one patient), and hypercalcemia (one patient). All serious TEAEs were resolved and considered unrelated to treatment. In addition, TEAEs of special interest were reported in four patients: hepatic enzyme increased (one patient), liver function test increased (two patients), transaminases increased (one patient). One patient had asymptomatic increases of blood creatine phosphokinase MB and troponin, both resolved.

STR1VE — GLOBAL

Phase 3 STR1VE Global Data as of May 31, 2019
The Global Phase 3 STR1VE clinical program includes ongoing, open-label, single-arm, single-dose, multi-center trials (STR1VE-US in the United States, STR1VE-EU in Europe and STR1VE-AP in Asia Pacific) designed to evaluate the efficacy and safety of a single, one-time IV infusion of Zolgensma in patients with SMA Type 1 who are less than six 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.

At the EPNS Congress, STR1VE-EU data will be presented side-by-side with STR1VE-US data. Collectively, these results demonstrate that a single, one-time treatment with Zolgensma has significant therapeutic benefit in prolonging event-free survival compared to natural history and rapidly improving motor function in patients with SMA Type 1.

Patients treated with Zolgensma continued to gain motor milestones. The mean follow-up time since dosing was 12.1 months in STR1VE-US and 4.2 months in STR1VE-EU. Eleven patients (50%) in the STR1VE-US study and two patients (6%) in the STR1VE-EU study achieved the ability to 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 the natural history of the disease.[3] Five of the six patients (83%) in STR1VE-US who reached 18 months of age (study completion) had achieved the milestone of sitting independently for 30 seconds (primary study endpoint). Additionally, one patient in the STR1VE-US study could pull to a stand and walk with assistance. In STR1VE-US, CHOP-INTEND scores increased by an average of 6.9 points one month, and 11.7 points three months after gene therapy treatment. In STR1VE-EU, scores increased by an average of 6.4 points one month, and 10.6 points three months after gene therapy treatment.

While the two trials represent the same patient population in terms of SMA type and entry criteria, e.g., age range and functional status, there were differences in the baseline characteristics in the patients from the two trials. In STR1VE-US the mean age at dosing was 3.7 months and the mean CHOP-INTEND score was 32. Whereas in STR1VE-EU, the mean age of dosing was 4.1 months and the mean CHOP-INTEND score was 28. Additionally, at the start of the trial in STR1VE-US, none of the patients needed nutritional or ventilatory support. In STR1VE-EU, nine patients needed nutritional support and seven needed ventilatory support. Lastly, none of the 25 STR1VE-US patients screened for AAV9 antibodies had exclusionary AAV9 antibody titers (>1:50), whereas six of the 40 patients screened in STR1VE-EU had titers >1:50. Upon rescreening, five STR1VE-EU patients were excluded due to elevated AAV9 antibodies.

"These updated data reinforce what we have seen in other Zolgensma studies, including survival of children with SMA Type 1 who would have in the past died or required permanent ventilation before the age of two," said Eugenio Mercuri, M.D., PhD., Department of Pediatric Neurology, Catholic University, Rome, Italy. "We are seeing further robust evidence of the potential of gene therapy to effectively halt motor neuron loss, help patients achieve motor milestones and alter the course of SMA with a one-time treatment."

STR1VE-US
Of the 22 patients enrolled in STR1VE-US, 20 were alive, without permanent ventilation, and continuing in the trial. Of 19 patients who had either reached 13.6 months of age or experienced an event, 17 patients (89.5%) survived without permanent ventilation. The mean age at the most recent visit was 15.8 months at an average follow-up time of 12.1 months. Natural history indicates that only 25% of Type 1 patients will survive event-free by the time they reach 13.6 months of age.[4] CHOP-INTEND scores increased by an average of 6.9 points one month and 11.7 points three months after gene therapy treatment.

In the STR1VE-US trial, one patient died from respiratory failure, which was deemed by the investigator and an independent Data Safety Monitoring Board to be unrelated to treatment. Additionally, after the safety data cutoff (March 8, 2019) one patient in the STR1VE-US study was determined by the investigator to have required ≥ 16 hours of non-invasive BiPAP ventilator support for ≥ 14 consecutive days at the time of withdrawal from the study. Based on this report from the investigator, AveXis will consider this patient as having required permanent ventilatory support at the time of discontinuation.

STR1VE-EU
As of May 31, of the 10 patients who had reached 10.5 months of age or experienced an event, nine (90%) survived without permanent ventilation. The mean age at the most recent visit was 8.2 months at an average follow-up time of 4.2 months. CHOP-INTEND scores increased by an average of 6.4 points one month (n=25) and 10.6 points three months (n=22) after gene therapy treatment.

As previously reported, one patient in the STR1VE-EU trial died prior to the March 8th safety data cutoff. According to the Coroner’s report, the immediate cause of death was hypoxic-ischemic brain damage with respiratory tract infection as the underlying cause. SMA Type 1 was indicated as the underlying cause for the respiratory tract infection. In addition, there was no evidence of an inflammatory CNS process or a toxic or a treatment-related brain damage.

Following the autopsy report findings, leukoencephalopathy, which was reassessed as hypoxic-ischemic brain damage, and respiratory distress are considered unrelated to the gene therapy by the investigator. The final autopsy report has indicated the gene therapy could have potentially contributed to the concurrent events of abnormal liver function tests (elevation of liver enzymes called transaminases), abnormal blood tests (low platelets) and low blood pressure. The serious adverse events (SAE) reports will be updated accordingly and submitted to the Health Authorities.

STR1VE Global Safety
Safety observations across the STR1VE Global data are comparable to those seen in the Phase 1 START trial. Adverse events of special interest, including elevated transaminases, platelet count decrease and thrombocytopenia, were transient and did not cause any long-term sequelae.

START

START Long-Term Follow-Up Data as of May 31, 2019

START was a Phase 1 study evaluating the safety and efficacy of a one-time IV infusion of Zolgensma in SMA Type 1 patients with the onset of clinical symptoms before six months of age. At the close of the 24-month study, all 12 patients in cohort 2 (targeted therapeutic dose) were alive and free of permanent ventilation. Without treatment, most of these patients would not survive past the age of two or would require permanent ventilation.[4] Ten of these 12 patients voluntarily enrolled in an ongoing observational long-term follow-up of the START study.

As of May 31, of the 10 patients who enrolled in the long-term follow-up study, all are alive and continue to maintain developmental milestones. Two patients, neither of whom have received treatment with nusinersen following Zolgensma infusion, gained the ability to stand with assistance. These milestones are in addition to the two START patients previously reported who are walking independently.

The mean age of patients was 4.2 years (range 3.7 – 5.0 years) and the mean time since gene therapy treatment was 3.9 years (range 3.5 – 4.6 years). Seven out of 10 patients (70%) are not currently receiving concomitant therapy with nusinersen. All patients have maintained or demonstrated improvements in ventilatory status. Six out of 10 patients (60%) do not require daily respiratory support.

There were no new treatment related SAEs and no adverse events of special interest occurred during the long-term follow up study. No fatal serious TEAEs have occurred during the parent study or long-term follow up study. Serious TEAEs were reported in six of 13 patients. The following serious TEAEs were reported in one or more patients: pneumonia (three patients), dehydration (two patients), acute respiratory failure (two patients), respiratory distress (two patients), bronchitis (one patient), cardiac arrest (one patient), gastroenteritis (one patient), hypoglycemia (one patient), respiratory failure (one patient).

About Zolgensma® (onasemnogene abeparvovec-xioi)
Zolgensma (onasemnogene abeparvovec-xioi) is a proprietary gene therapy approved by the U.S. 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 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.[5,6] The incidence of SMA is approximately 1 in 10,000 live births and it is the leading genetic cause of infant mortality.[3,6] 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.[4]

Zolgensma in the United States

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 ≥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 “potential,” “can,” “will,” “plan,” “expect,” “anticipate,” “look forward,” “believe,” “committed,” “investigational,” “pipeline,” “launch,” or similar terms, or by express or implied discussions regarding potential marketing approvals, new indications or labeling for the investigational or approved 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 the investigational or approved 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.

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 108,000 people of more than 140 nationalities work at Novartis around the world. Find out more at www.novartis.com.

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**Event-free survival is defined by the avoidance of the combined endpoint of either (a) death or (b) permanent ventilation, which is defined by tracheostomy or by the requirement of ≥ 16 hours of respiratory assistance per day (via non-invasive ventilatory support) for ≥ 14 consecutive days in the absence of an acute reversible illness, excluding perioperative ventilation.*

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