AveXis data reinforce effectiveness of Zolgensma® in treating spinal muscular atrophy (SMA) Type 1

- Ph 3 STR1VE data show prolonged event-free survival, early and rapid increases in CHOP-INTEND and significant milestone achievement in SMA Type 1, consistent with START trial
- First-in-human biodistribution data show transduction in intended CNS targets and widespread SMN expression comparable to tissue from unaffected control
- More than 150 patients treated with Zolgensma, only 5% of screened patients up to 5 years old excluded due to AAV9 antibody titers greater than 1:50

Basel, April 16, 2019 – AveXis, a Novartis company, today announced that interim data from its Phase 3 STR1VE trial of Zolgensma® (onasemnogene abeparvovec-xioi; AVXS-101) in spinal muscular atrophy (SMA) Type 1 showed prolonged event-free survival, an early and rapid increase in CHOP-INTEND scores and significant milestone achievement compared to untreated natural history, consistent with data from the pivotal Phase 1 START trial. First-in-human biodistribution individual case study data from STR1VE showed Zolgensma successfully transduced intended targets in the central nervous system (CNS) and provided widespread SMN expression comparable to tissue from unaffected individual. Additional data presented showed 95 percent of patients screened across the Zolgensma clinical development program and Managed Access Program were not excluded from treatment due to elevated AAV9 antibody titers greater than 1:50. These data were presented today at the 2019 Muscular Dystrophy Association (MDA) Clinical and Scientific Conference in Orlando, Florida.

“These STR1VE data reinforce what was seen in the pivotal Phase 1 START trial, including trends toward prolonged survival and milestone achievement never seen in the natural history of the untreated disease,” said Olga Santiago, MD, Chief Medical Officer, AveXis. “With a patient population and baseline characteristics closely matched to the START trial, these data build upon the body of evidence supporting the use of Zolgensma for SMA Type 1.”

Interim Phase 3 STR1VE Data as of September 27, 2018

STR1VE is an ongoing, open-label, single-arm, single-dose, multi-center trial designed to evaluate the efficacy and safety of a one-time intravenous infusion of Zolgensma in patients with SMA Type 1 who are less than six months of age at the time of gene therapy. The study was designed to enroll the broadest possible population of SMA Type 1 patients with one or two copies of the SMN2 backup gene and who have bi-allelic SMN1 gene deletion or point mutations. These criteria are well-matched to the patient population that was enrolled in the pivotal Phase 1 START trial while potentially providing treatment to some of the rarer subpopulations on an exploratory basis. STR1VE is projected to complete in 2020.

As of September 27, 2018, 21 of 22 (95 percent) patients were alive and event-free. The median age was 9.5 months, with 6 of 7 (86 percent) patients who could have reached 10.5 months of age or older surviving event-free. Untreated natural history indicates that 50
percent of babies with SMA Type 1 will not survive or will require permanent ventilation by the time they reach 10.5 months of age.3

Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores increased by an average of 7.0 points one month after gene transfer and 11.8 points three months after gene transfer, reflecting improvement in motor function from baseline. These data are similar to CHOP-INTEND achievement by the proposed therapeutic dose cohort (Cohort 2) in the pivotal START trial, which demonstrated mean increases of 9.8 and 15.4 points at the same time points, respectively. Early CHOP-INTEND increases appear to be associated with eventual milestone achievement.

Preliminary assessments of patients treated with Zolgensma showed the achievement of motor milestones, including three patients who could sit without support for at least 30 seconds as of September 27, 2018 (median of 9.4 months), increasing to eight patients who could achieve the same milestone as of December 31, 2018 (median age of 12.5 months).

<table>
<thead>
<tr>
<th>Milestone Achieved, n (%)a</th>
<th>Phase 3 STRIVE Study, n=22</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>September 27, 2018</td>
</tr>
<tr>
<td>Holds head erect ≥3 seconds without supportb</td>
<td>12 (54.5)c</td>
</tr>
<tr>
<td>Turns from back to both right and left sidec</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Sits without support for ≥30 secondsd</td>
<td>3 (13.6)</td>
</tr>
<tr>
<td>Stands with assistancee</td>
<td>0</td>
</tr>
<tr>
<td>Median duration of follow-up at data cut</td>
<td>5.5 months</td>
</tr>
<tr>
<td>Median age at data cut</td>
<td>9.4 months</td>
</tr>
<tr>
<td>Patients older than 12 months, n (%)</td>
<td>5 (22.7)</td>
</tr>
</tbody>
</table>

Bayley-III, Bayley Scales of Infant and Toddler Development, V.3; SMA1, spinal muscular atrophy type 1.

- Developmental milestones were confirmed by video;
- In accordance with Bayley-III, gross motor subtest item #4;
- One patient reached the milestone of head control at the first screening visit (prior to dosing); In accordance with Bayley-III, gross motor subtest gross motor subtest item #20;
- In accordance with Bayley-III, gross motor subtest item #26;
- In accordance with Bayley-III, gross motor subtest item #33 — supports own weight for ≥2 seconds.

Safety observations are comparable to those seen in the pivotal 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. 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, with a 27-point increase in CHOP-INTEND from baseline five months post-infusion.

AveXis is grateful to the courageous patients and families who participate in our trials, enabling us to further our efforts to make a meaningful difference in the lives of patients with rare genetic diseases.

**Biodistribution of Zolgensma**

First-in-human analysis of tissues from the deceased patient showed that Zolgensma successfully transduced tissues of the CNS, including brain and spinal cord motor neurons, and showed widespread expression of SMN comparable to tissue from an unaffected individual and clearly distinguishable from untreated SMA patient samples.

Evaluation of Zolgensma transgene DNA, mRNA and SMN protein biodistribution was assessed by ddPCR™, RT-PCR and immunohistochemical SMN protein staining, respectively. The results of these analyses consistently demonstrated that Zolgensma vector genomes, RNA transcripts and SMN protein were broadly distributed and detected in all organs tested. Zolgensma vector genomes per diploid genome were detected in cervical, thoracic, lumbar and sacral regions. Correspondingly, in each of these spinal cord regions, SMN protein was expressed in spinal motor neurons at levels similar to non-SMA Type 1
tissues. SMN protein expression was also detected in cortical and subcortical regions of the motor cortex and medulla. Both Zolgensma and non-SMA Type 1 tissues were clearly distinct from tissues from untreated SMA Type 1 patients.

Analysis of the motor neuron marker choline acetyltransferase (ChAT) demonstrated that motor neurons were abundant and of normal size and shape in the Zolgensma-treated patient tissue. In contrast, ChAT motor neuron staining in the non-treated SMA Type 1 patient tissue was sparse, suggesting the motor neurons were sick and/or dying.

These human data support the mechanism of action initially identified in non-human non-clinical studies in murine and non-human primate models, that a single intravenous administration of Zolgensma is able to restore SMN expression to motor neurons that lack a functional SMN1 gene, thereby addressing the root cause of SMA.

AAV9 Antibody Data
Zolgensma introduces a functional copy of the SMN gene using the adeno-associated viral vector 9 (AAV9). AAV9 is a common virus not known to cause disease in humans, and there is a low prevalence of anti-AAV antibodies in young children, lowering the probability of immunological reaction to the AAV9 vector.4,5,6

Approximately five percent of patients (9/177) up to five years of age who underwent screening for Zolgensma were excluded from treatment across the clinical development program (including intravenous and intrathecal administration) and Managed Access Program due to elevated AAV9 antibody titers greater than 1:50. Of those screened, more than 150 patients have been dosed with Zolgensma to date.

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 monogenic root cause of SMA and prevent further muscle degeneration by providing a copy of the human SMN gene to halt disease progression through rapid and sustained SMN protein expression. Zolgensma represents the first in a proprietary platform to treat rare, monogenic diseases using gene therapy. In December, 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.

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 Zolgensma and the other 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 or the other 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 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.
2. An event is defined as either death or at least 16 hours per day of required ventilation support for breathing for 14 consecutive days in the absence of acute reversible illness or perioperative change.

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