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Zolgensma® data shows rapid, significant, clinically meaningful benefit in SMA including prolonged event-free survival, motor milestone achievement and durability now up to 5 years post-dosing

- *Interim SPR1NT data showed presymptomatic babies with SMA treated with Zolgensma® (onasemnogene abeparvovec-xioi) soon after birth achieved age-appropriate motor milestones*
- *In addition to meeting both co-primary efficacy endpoints, nine of 22 patients in the completed pivotal STR1VE-US study demonstrated the "ability to thrive," a stringent composite endpoint remarkable compared to untreated children with SMA Type 1*
- *Ongoing START long-term follow-up study (cohort 2) demonstrated sustained durability of Zolgensma, including the achievement and maintenance of milestones in the follow up period, now up to 5 years post-dosing and up to 5+ years of age*
- *Cumulative safety data from 335 patients treated with Zolgensma indicate a safety profile consistent with previously-reported safety information*

Basel, March 24, 2020 – AveXis, a Novartis company, today announced a one-time infusion of Zolgensma® (onasemnogene abeparvovec-xioi) showed rapid, significant and clinically meaningful therapeutic benefit in patients with spinal muscular atrophy (SMA) across a range of studies, including in patients treated presymptomatically, and sustained durability in patients now up to five years post-dosing and some patients more than five years of age. The STR1VE-US study findings are being presented today during a virtual Clinical Trial Session conducted by the Muscular Dystrophy Association (MDA), scheduled after the 2020 MDA Annual Conference was cancelled due to COVID-19. The accepted posters for SPR1NT, START long-term follow up and cumulative safety data will be published online by MDA in the coming weeks.

Interim data from the ongoing SPR1NT study continue to show patients achieved age-appropriate motor milestones when treated with Zolgensma presymptomatically. Most patients (7/8) with two copies of *SMN2* who achieved the ability to sit independently did so within the World Health Organization window of normal development. The six remaining patients in this cohort of 14 patients have not yet passed the developmental window. The importance of independent sitting is that it allows for the potential development and integration of the cognitive, sensory and motor skills that are important for functional independence and social development. Additionally, nearly all patients were fed orally and required no feeding support. Most remained within the age-appropriate weight range. No patients required ventilatory support of any kind.

“SMA is a disease that robs babies of the ability to talk, eat, sit up and even breathe. In complete contrast to the natural course of the disease, patients who received Zolgensma soon after birth before the onset of symptoms are achieving age-appropriate motor milestone development – an extraordinary outcome for SMA patients,” said Olga Santiago, M.D., Chief Medical Officer, AveXis. “These SPR1NT data demonstrate the truly transformational impact a one-time dose of gene therapy can have, and further underscore the importance of newborn screening and early intervention to alter the course of the disease.”

SMA Type 1 patients experienced rapid, sustained and clinically meaningful improvements in motor function in the completed pivotal STR1VE-US study. In STR1VE-US, nearly all (91%) patients met the co-primary efficacy endpoint of event-free survival at 14 months, and more than half (59%) of patients met the co-primary efficacy endpoint of sitting for ≥30 seconds at 18 months of age, a milestone never achieved in the natural history of SMA Type 1. Importantly, nine of 22 patients demonstrated the “ability to thrive” at 18 months of age. As the goal of treatment for SMA Type 1 moves beyond survival and motor milestone achievement, the STR1VE-US trial is the first to incorporate this stringent composite endpoint – inclusive of functions of swallowing, feeding and age-appropriate weight maintenance – and demonstrate remarkable achievements in symptomatic patients with SMA Type 1, the most prevalent form of the disease accounting for 60% of SMA diagnoses.[1,2]

New data from the START long-term follow-up study continue to demonstrate the durability of a single, one-time dose of Zolgensma in patients now up to five years post-dosing and some patients more than five years of age. All patients in this study who received the therapeutic dose were alive and free of permanent ventilation and continued to maintain developmental milestones, including two patients who achieved the new milestone of standing with assistance during the long-term follow-up period.

Cumulative safety data from patients treated with intravenous Zolgensma in clinical trials, U.S. managed access program, the RESTORE global registry and commercial experience were consistent with previously-reported safety information. Reported adverse events (AEs) were monitorable and manageable, and the overall benefit-risk safety profile remains favorable.

“The bar for treatment efficacy in SMA Type 1 patients has been raised beyond event-free survival and motor milestone achievement, and the expectation is now that these patients maintain the ability to thrive, an unprecedented and challenging endpoint,” said Lisa Deschamps, Chief Business Officer, AveXis. “Further, with hundreds of patients now treated, including some more than five years post-treatment and more than five years old, these new data further reinforce the profound benefit a one-time dose of Zolgensma has on SMA patients.”

SPR1NT Data as of December 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 presymptomatic patients with SMA and two or three copies of *SMN2* who are <=6 weeks of age. Fourteen patients with two copies of *SMN2* and 15 patients with three copies of *SMN2* were treated.

As of December 31, 2019, the mean age of patients in the two-copy cohort was 11.2 months (6.0-18.6 months of age) at last follow up. For the three-copy cohort, the mean age was 9.7 months (3.3-15.1 months of age). Nearly all patients were alive and free of ventilatory support of any kind. All patients were fed orally and required no feeding support. Most remained within (at or above third percentile) the gender and age-appropriate weight range.

All patients in the two-copy cohort achieved or maintained a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) score of ≥50. Thirteen patients achieved a CHOP INTEND score of ≥58, including nine patients who achieved a score of ≥58 for three consecutive visits. According to natural history, untreated patients with SMA Type 1 almost never achieve a CHOP INTEND score ≥40.

Of patients with two copies of *SMN2*, eight patients so far were able to sit independently for at least 30 seconds (range 5.7–11.8 months of age), with seven of these achieving independent sitting within the range of normal development. Four patients so far were able to walk independently (range 12.2–18.3 months of age). Patients in this cohort who have not achieved these milestones yet are still within the normal age development window for these milestones.

Of the patients with three copies of *SMN2*, four patients were able to stand alone without support for at least three seconds (9.5–12.4 months of age) and three patients were able to walk independently (12.2–15.1 months of age), all achieved within the range of normal development. Patients in this cohort who have not achieved these milestones yet are still within the normal age development window for these milestones.

All patients experienced at least one adverse event (AE) after dosing of which 17 were considered treatment-related. Overall, the most common AEs were pyrexia (30%), upper respiratory tract infection (23%), constipation (17%), and nasopharyngitis (17%), which are consistent with events experienced by children with SMA and the general population. Six patients were reported to have serious adverse events (SAEs), none of which were assessed by the investigator and AveXis to be related to treatment.

STR1VE-US – Study Complete
STR1VE-US is a part of the global Phase 3 STR1VE clinical program. This includes 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 symptomatic 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.

In STR1VE-US, 20 of 22 patients (91%) met the co-primary efficacy endpoint of event-free survival at 14 months, and 13 of 22 patients (59%) met the co-primary efficacy endpoint of functional sitting for ≥30 seconds at 18 months of age. Thirteen patients (59.1%) achieved the developmental milestone of functional independent sitting for ≥30 seconds ($P<0.0001$ vs natural history) at the 18 months of age study visit. A 14th patient achieved the milestone of sitting independently for 30 seconds at 16 months of age, but this milestone was not confirmed at the month 18 visit. Fifteen patients (68.2%) did not require non-invasive ventilatory support at any point during the study. Eighteen of 22 patients (81.8%) did not use ventilatory support (as assessed by Trilogy BiPAP data) at 18 months of age.

STR1VE-US is the first trial in symptomatic patients with SMA Type 1 to incorporate the stringent composite endpoint of “ability to thrive.” Of the 22 patients, nine (40.9%) achieved this co-secondary endpoint at 18 months of age ($P<0.0001$ vs natural history), including 19 patients (86.4%) who did not receive nutrition through any feeding tube or other non-oral method, 14 patients (63.6%) who maintained weight (greater than third percentile) consistent with gender and age and 12 patients (54.5%) who were able to tolerate thin liquid.

In STR1VE-US, patients achieved rapid and sustained improvement in motor function unseen in natural history. CHOP INTEND scores increased by an average of 6.9 points at one month (N=22), 11.7 points at three months (N=22) and 14.6 points at six months (N=20) after gene therapy treatment. Twenty-one patients (95.5%) achieved a CHOP INTEND score ≥40, and 14 (63.6%) achieved a CHOP INTEND score ≥50.

No new deaths have been reported. As previously reported, one patient died from respiratory failure six months after receiving Zolgensma, which was assessed as due to underlying SMA and unrelated to treatment by the investigator and an independent Data Safety Monitoring Board. As previously reported, one patient discontinued (withdrew consent) at 11.9 months of age; this patient required permanent ventilation prior to withdrawal of consent. All 22 treated patients were reported to have at least one AE, of which 12 were considered by the investigator to be related to Zolgensma. Ten patients were reported to have SAEs, three of

which were assessed by the investigator and AveXis to be related to treatment. Overall, the most frequently reported AEs were pyrexia (54.5%), upper respiratory tract infection (50.0%), constipation (40.9%), and scoliosis (40.9%), which are consistent with events experienced by children with SMA and the general population. AEs were manageable and consistent with the known safety profile of Zolgensma.

START Long-Term Follow-Up (LTFU) Data as of December 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. Ten of these 12 patients voluntarily enrolled in an ongoing observational long-term follow-up of the START study.

START LTFU is an ongoing, observational, long-term follow-up study of patients who completed START and electively enrolled in the study. As of December 31, of the 10 patients from cohort 2 who enrolled in LTFU, all are alive and free of permanent ventilation. No previously achieved motor milestone has been lost during the follow up period. Two patients gained the new milestone of standing with assistance (neither of whom have received treatment with nusinersen) during the follow up period.

The mean age of patients was 4.8 years (range 4.3–5.6 years) and the mean time since gene therapy treatment was 4.5 years (range 4.1–5.2 years). Six out of 10 patients (60%) are not currently receiving concomitant therapy with nusinersen. No patient who was free of ventilatory support at the end of the study has initiated new mechanical respiratory support during the follow up period. Six out of the 10 patients (60%) do not require regular, daily respiratory support more than four years after dosing.

There were no new treatment related SAEs and no AEs of special interest occurred during the long-term follow up study.

Cumulative Safety Data as of December 31, 2019
Safety data from post-marketing experience (192 patients) was consistent with previously observed safety data across all clinical investigations of IV Zolgensma (100 patients) and the U.S. managed access program and the RESTORE global patient registry (43 patients). Data reviewed from 335 patients indicated that nearly all patients experienced AEs, however, most were not serious and were unrelated to treatment. In general, AEs associated with Zolgensma are monitorable and manageable: (1) liver transaminase elevations should be monitored through liver function tests and managed through the use of prophylactic prednisolone; (2) thrombocytopenia events have been transient and resolved without medical intervention and can be monitored through platelet counts; and (3) reported cardiac events have been heart rate changes and laboratory abnormalities without associated clinical sequelae. Troponin I should be monitored.

A thorough analysis has been completed to assess sensory abnormalities indicative of dorsal root ganglia inflammation. While this remains a preclinical finding and clinical events have not been reported, AveXis has implemented a monitoring plan in clinical trials to evaluate and characterize this further.

No new deaths reported; two deaths were previously reported after Zolgensma dosing (STR1VE-US and STR1VE-EU), both of which were considered unrelated to treatment based on autopsy findings.

Novartis will conduct a conference call with investors to discuss this news release on Monday, March 30, 2020 at 3 p.m. Central European Time and 9 a.m. Eastern Time. A simultaneous webcast of the call for investors and other interested parties may be accessed by visiting the

Novartis website. A replay will be available after the live webcast by visiting https://www.novartis.com/investors/event-calendar.

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 two 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 the company's proprietary platform to treat rare, monogenic diseases using gene therapy. Approximately 400 patients have been treated with Zolgensma, including clinical trials, commercially and through the managed access program in the U.S. The therapy was recently approved by the Japanese Ministry of Health, Labour and Welfare and AveXis is pursuing registration in close to three dozen countries, with a Committee for Medicinal Products for Human Use opinion expected in 1Q 2020 and regulatory decisions anticipated in Switzerland, Canada and Australia in late 2020 or early 2021.

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 Généthon 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 Spinal Muscular Atrophy
SMA is the leading genetic cause of infant death.[3] If left untreated, SMA Type 1 leads to death or the need for permanent ventilation by the age of two in more than 90% of cases.[4]
SMA is a rare, genetic neuromuscular disease caused by a lack of a functional *SMN1* gene, resulting in the rapid and irreversible loss of motor neurons, affecting muscle functions, including breathing, swallowing and basic movement.[5] 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.[6] This is especially critical in SMA Type 1, where motor neuron degeneration starts before birth and escalates quickly. Loss of motor neurons cannot be reversed, so SMA patients with symptoms at the time of treatment will likely require some supportive respiratory, nutritional and/or musculoskeletal care to maximize functional abilities.[7]

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,” “may,” “could,” “would,” “expect,” “anticipate,” “seek,” “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, or regarding potential future revenues from Zolgensma. 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, 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 Zolgensma will be commercially successful in the future. In particular, our expectations regarding Zolgensma 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, economic and business conditions, including the effects of and efforts to mitigate pandemic diseases such as COVID-19; safety, quality, data integrity 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 the world's leading gene therapy company, redefining the possibilities for patients and families affected by life-threatening genetic diseases through our innovative gene therapy platform. Founded in 2013 and headquartered in Bannockburn, IL, the goal of AveXis' cutting-edge science is to address the underlying, genetic root cause of diseases. AveXis pioneered foundational research, establishing AAV9 as an ideal vector for gene transfer in diseases affecting the central nervous system, laying the groundwork to build a best-in-class, transformational gene therapy pipeline. AveXis received its first U.S. Food and Drug Administration approval in May 2019 for the treatment of spinal muscular atrophy (SMA). AveXis is also developing therapies for other genetic diseases, including Rett syndrome, a genetic form of amyotrophic lateral sclerosis (ALS) SOD1 and Friedreich's ataxia. 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 nearly 800 million people globally and we are finding innovative ways to expand access to our latest treatments. About 109,000 people of more than 145 nationalities work at Novartis around the world. Find out more at https://www.novartis.com.

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