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MEDIA RELEASE • COMMUNIQUE AUX MEDIAS • MEDIENMITTEILUNG

Novartis announces FDA filing acceptance and Priority Review of AVXS-101, a one-time treatment designed to address the genetic root cause of SMA Type 1

- *The AVXS-101, now known as ZOLGENSMA® (onasemnogene abeparvovec-xxxx)[1], filing is supported by data from the START trial which demonstrated a dramatic increase in survival and transformative improvement in achievement of developmental milestones compared to the natural history of SMA Type 1*[2]

- *SMA Type 1 is a progressive neuromuscular disease and the leading cause of genetic mortality in infants globally* [3]

- *ZOLGENSMA® represents the first in a proprietary platform to treat rare, monogenic diseases using gene replacement therapy – technology that replaces a missing or defective gene with a functional copy to correct the underlying cause of genetic disease*

Basel, December 3, 2018 – Novartis today announced that the U.S. Food and Drug Administration (FDA) has accepted the company's Biologics License Application (BLA) for AVXS-101, now known as ZOLGENSMA® *(onasemnogene abeparvovec-xxxx)[1]*, an investigational gene replacement therapy for the treatment of spinal muscular atrophy (SMA) Type 1. ZOLGENSMA is designed to address the genetic root cause of SMA Type 1, a deadly neuromuscular disease with limited treatment options. ZOLGENSMA previously received Breakthrough Therapy designation and has been granted Priority Review by the FDA, with regulatory action anticipated in May 2019.

SMA is caused by a defective or missing *SMN1* gene.[4] Without a functional *SMN1* gene, infants with SMA Type 1 rapidly lose the motor neurons responsible for muscle functions such as breathing, swallowing, speaking and walking.[3] Left untreated, a baby's muscles become progressively weaker eventually leading to paralysis or death, in most cases by his or her second birthday.[5] Delivered as a single, one-time infusion, this breakthrough technology works by replacing the missing or defective *SMN1* gene with a functional copy that makes SMN protein, thereby improving motor neuron function and survival.[2]

"This important step by the FDA brings us ever closer to delivering ZOLGENSMA to patients with SMA Type 1. Babies affected by this rare disease are currently faced with debilitating disease progression and lifelong invasive chronic treatment. As a one-time infusion that addresses the genetic root cause of SMA without the need for repeat dosing, ZOLGENSMA represents a potentially significant therapeutic advance for these patients and their families," said David Lennon, president of AveXis. "The introduction of one-time, potentially curative therapies will require rethinking how our healthcare system manages diagnosis, treatment, care and associated costs for patients with genetic disease. Novartis and AveXis are proud to lead the way toward a modern healthcare system built on the tremendous value of truly innovative and transformative medicines that could bend the curve of life. We are committed to flexibly partnering with healthcare stakeholders to ensure appropriate access to our medicines."

In the START trial, all 15 patients infused with ZOLGENSMA were alive and without the need for permanent ventilation* at 24 months. Ninety-two percent (11/12) of patients who received

the proposed therapeutic dose of ZOLGENSMA could sit unassisted for ≥5 seconds, a milestone never achieved in the natural history of SMA Type 1. Natural history indicates that more than 90 percent of untreated patients with SMA Type 1 will die or require permanent ventilation by 24 months of age.[5] Patients who voluntarily enrolled in an ongoing observational long-term follow-up of the START trial have maintained their developmental motor milestones – including patients who are four years post infusion – with some achieving additional motor milestones. The most commonly observed side effect in the ZOLGENSMA clinical trial was elevated liver enzymes.[2,6]

In Japan, where ZOLGENSMA has SAKIGAKE Designation, a decision by regulators on the New Drug Application (J-NDA) is expected in the first half of 2019. In Europe, where ZOLGENSMA has PRIME (PRIority MEdicines) designation, a decision by regulators on the Marketing Authorization Application (MAA) is expected in mid-2019. The SAKIGAKE and PRIME designations are comparable to the FDA's Breakthrough Therapy designation. These regulatory applications are based primarily on data from the START trial.

Priority Review designation means the FDA's goal is to take action on an application within six months, compared to 10 months under standard review.

About 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.[3] The incidence of SMA is approximately one in 10,000 live births and is the leading genetic cause of infant mortality.[7] The most severe form of SMA is Type 1, a lethal genetic disorder characterized by 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.[3,5]

About ZOLGENSMA
ZOLGENSMA ([onasemnogene abeparvovec-xxxx[1];] AVXS-101) is a proprietary gene replacement 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 replacing the defective and/or loss of the primary SMN gene (*SMN1*).

About the START Trial[2,6]
START was a Phase 1 study evaluating safety and efficacy of ZOLGENSMA in SMA Type 1 patients genetically tested to confirm bi-allelic *SMN1* deletions, 2 copies of survival motor neuron 2 (*SMN2*), negative findings for the c.859G>C modification in exon 7 and with the onset of clinical symptoms before 6 months of age. ZOLGENSMA was delivered intravenously during a single-dose infusion in patients 0.9 to 7.9 months of age. Two cohorts were dosed: Cohort 1 (n=3) received the low dose used in this study and Cohort 2 (n=12) received the high dose used in this study.

At the 24-month follow up, all 15 patients (100%), who were over all 24 months of age, were event-free, as opposed to only 8% of patients in a natural history study. This indicates a significant and clinically meaningful increase in overall survival for patients infused with ZOLGENSMA when compared to untreated patients. At two years following infusion, no patient deaths were reported. The most commonly observed side effect in the ZOLGENSMA clinical trial was elevated liver enzymes.

The reported study outcomes reflect Cohort 2 and includes follow-up of all patients out to 24 months following ZOLGENSMA infusion. Patients in Cohort 2 consistently achieved and maintained key developmental motor milestones. At 24 months of follow-up post-infusion, 11 patients (91.7%) were able to hold their head erect for ≥ 3 seconds and sit without support for ≥ 5 seconds, 10 patients (83.3%) were able to sit without support for ≥ 10 seconds, 9 patients (75.0%) were able to sit without support for ≥ 30 seconds and 2 patients each (16.7%) were able to stand alone, walk with assistance and walk alone.

Of the 10 patients in Cohort 2 that were not using non-invasive ventilation (NIV) at baseline, 7 were free of daily NIV use at 24 months of follow-up. Nearly all patients experienced common childhood respiratory illnesses that, in children with SMA Type 1, typically result in tracheostomy or death. All patients survived respiratory hospitalizations without tracheostomy or the need for permanent ventilation.

Nutritional gains were also observed. In Cohort 2, seven patients did not receive enteral feeding prior to ZOLGENSMA infusion. One of these 7 patients had nutritional support post-ZOLGENSMA infusion to assist wound healing following a difficult recovery from scoliosis surgery but was also feeding orally. Four of the 5 patients in Cohort 2 who received enteral feeding prior to ZOLGENSMA infusion were able to feed orally at end of study; thus, a total of 11 of the 12 patients in Cohort 2 were able to feed orally, 6 exclusively.

Patients receiving the therapeutic dose achieved statistically significant motor function improvements by month 1 and month 3; Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) mean increases from baseline were 9.8 points ($n=12$, $P < 0.001$) and 15.4 points ($n=12$, $P < 0.001$), respectively. Motor function improvements were sustained over time in patients infused with ZOLGENSMA. Eleven of twelve (91.7%) Cohort 2 patients achieved a ≥ 50 CHOP-INTEND during the 24-month study period. Early intervention and dose appear to positively affect the response. In general clinical practice, untreated SMA Type 1 children 6 months of age or older do not surpass a score of 40 points on the CHOP-INTEND. Furthermore, an average decline of 10.7 points between the ages of 6 and 12 months were reported amongst untreated infants followed as part of a prospective natural history.

Cohort 2 patients who are currently voluntarily enrolled in an ongoing observational long-term follow-up of this study have maintained their developmental motor milestones – including patients who are four years post infusion – with some achieving additional motor milestones. Four patients attained new milestones, including 2 patients who sat unassisted for ≥30 seconds and two patients were able to stand with support.

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 labelling 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; 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.

**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.*[2]

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 its 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 nearly 1 billion people globally and we are finding innovative ways to expand access to our latest treatments. About 125 000 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-xxxx) has been provisionally approved by the FDA for the investigational product AVXS-101 (with a four-letter suffix to be added), but the product itself has not received marketing authorization or BLA approval from any regulatory authorities.
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5 Finkel RS, McDermott MP, Kaufmann P. et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology. 2014;83(9):810-7.
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