Novartis International AG
Novartis Global Communications
CH-4002 Basel
Switzerland

http://www.novartis.com

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Novartis announces AVXS-101 intrathecal study update

- *FDA placed a partial hold on AVXS-101 intrathecal clinical trials for SMA patients based on findings in a small pre-clinical animal study*
- *Adverse events that might be expected from the pre-clinical findings have not been seen in a thorough review of human safety data from all available sources to date*
- *Zolgensma® (onasemnogene abeparvovec-xioi) also known as AVXS-101 intravenous administration is not impacted and remains available in the US*
- *Novartis is working with FDA to determine next steps to release partial hold and resume dosing in the AVXS-101 intrathecal trials*

Basel, October 30, 2019 – Novartis today announced the United States Food & Drug Administration (FDA) placed a partial hold on clinical trials for intrathecal administration of AVXS-101. The announcement follows an AveXis communication to health authorities and clinical trial investigators based on findings from a small, AveXis-initiated pre-clinical study in which animal findings showed dorsal root ganglia (DRG) mononuclear cell inflammation, sometimes accompanied by neuronal cell body degeneration or loss. This partial hold by the FDA does not impact marketed Zolgensma® or AVXS-101 intravenous (IV) clinical trials.

AveXis is studying AVXS-101 intrathecal administration in patients with spinal muscular atrophy (SMA) Type 2. The partial hold impacts enrollment in the high dose cohort of the STRONG trial, an ongoing, open-label, dose-comparison, multi-center trial designed to evaluate the efficacy, safety and tolerability of one-time intrathecal administration of AVXS-101. The low and mid dose cohort enrollment has previously been completed and interim results have been presented.

The clinical significance of the DRG inflammation observed in this pre-clinical animal study is not known and was not seen in prior animal studies with AVXS-101. DRG inflammation can be associated with sensory effects. Of note, we have completed a thorough review of human safety data from all available sources to date and no adverse effects related to sensory changes have been seen in AVXS-101 intrathecal or Zolgensma. We are working with health authorities to confirm further guidance to clinical investigators.

We will continue to closely monitor for any reports of related safety events in patients. We remain confident that the overall benefit-risk profile for patients on treatment is favorable and we continue to advance our AVXS-101 intravenous clinical studies. We will work diligently with FDA to identify any additional actions necessary to resume dosing in the AVXS-101 intrathecal clinical trials.

AveXis and Novartis remain committed to researching and developing gene therapies for SMA, a rare and devastating genetic disease.

About AVXS-101 Intrathecal Administration
Investigational IT administration of AVXS-101 is currently being evaluated in patients with SMA Type 2 in a Phase 1/2 clinical trial.

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.

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.[3,4] The incidence of SMA is approximately 1 in 10,000 live births and it is the leading genetic cause of infant mortality.[1,4] 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.[5] More than 30% of patients with SMA Type 2 will die by age 25.2

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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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Novartis Media Relations
E-mail: media.relations@novartis.com

Eric Althoff
Novartis US External Communications
+1 646 438 4335 (mobile)
eric.althoff@novartis.com

Samantha Schwarz
Senior Director, Corporate Communications, AveXis
+1 312 925 6315 (mobile)
sschwarz439@avexis.com

Antonio Ligi
Novartis Global External Communications
+41 61 324 1374 (direct)
antonio.ligi@novartis.com

Novartis Investor Relations
Central investor relations line: +41 61 324 7944
E-mail: investor.relations@novartis.com

Central		North America	
Samir Shah	+41 61 324 7944	Sloan Simpson	+1 862 778 5052
Pierre-Michel Bringer	+41 61 324 1065	Cory Twining	+1 862 778 3258
Thomas Hungerbuehler	+41 61 324 8425		
Isabella Zinck	+41 61 324 7188		