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MEDIA & INVESTOR RELEASE

Novartis announces lift of partial clinical trial hold and plans to initiate a new, pivotal Phase 3 study of intrathecal OAV-101 in older patients with SMA

Ad hoc announcement pursuant to Art. 53 LR

- *FDA concluded that OAV-101 intrathecal (IT) clinical program may proceed based on data from nonclinical toxicology study*
- *New Phase 3 STEER study will evaluate efficacy, safety, and tolerability of OAV-101 IT in treatment-naïve patients with SMA Type 2 aged between 2 and 18 years old, the first to study gene therapy in this patient population*
- *STEER will build upon the OAV-101 IT STRONG study which demonstrated significant increases in HFMSE scores and a clinically meaningful response in patients with SMA Type 2 aged between ≥2 years and <5 years old*
- *OAV-101 IT under investigation as a one-time, single-dose, treatment option for older patients with SMA*

Basel, August 3, 2021 — Novartis today announced that the U.S. Food and Drug Administration (FDA) has determined that OAV-101 intrathecal (IT) clinical trials for spinal muscular atrophy (SMA) patients may proceed, thereby lifting the partial clinical trial hold initiated in October 2019. The decision to lift the hold was based on data from Novartis' comprehensive nonclinical toxicology study in non-human primates (NHP) that addressed all issues identified, including questions of dorsal root ganglia (DRG) injury following IT administration.

Following this decision and input from the FDA and European Medicines Agency (EMA), Novartis now plans to initiate STEER, a global pivotal Phase 3 registration-enabling study to evaluate the clinical efficacy, safety, and tolerability of OAV-101 IT in treatment naïve patients who are between two and 18 years of age, able to sit, but have never walked. While disease progression is slower in patients with later-onset SMA, there are significant unmet needs.

"We are very pleased that our comprehensive nonclinical data package has addressed all issues identified related to DRG toxicity and the FDA has reached the decision that we may proceed with our OAV-101 IT clinical trial program and initiate the STEER trial," said Shephard Mpofu, M.D., SVP, Chief Medical Officer, Novartis Gene Therapies. "We believe that all patients diagnosed with SMA should be able to benefit from the transformative impact of gene therapy and we remain confident that investigational OAV-101 IT is a viable potential treatment path for older patients who often have ongoing unmet needs, and for whom a one-time treatment could be especially compelling."

STEER will build upon the Phase 1/2 STRONG study which showed that treatment with OAV-101 IT led to significant increases in Hammersmith Functional Motor Scale-Expanded

(HFMSE) scores and a clinically meaningful response in older patients between ≥2 years and <5 years old with SMA Type 2.

Additionally, STEER will add to the clinical data and emerging real-world evidence for the use of gene therapy to treat SMA. Our intravenous formulation, Zolgensma® (onasemnogene abeparvovec) is approved in 41 countries. More than 1,400 patients have been treated with Zolgensma IV globally, including in the European Union, South Korea and Canada, where regulatory approval includes dosing guidance for babies and young children up to 21kg.

“We are very pleased to see that a plan has been reached from Novartis, the FDA and EMA working together to move this IT approach forward,” said Kenneth Hobby, President, Cure SMA. “This route of administration has the potential to open up access for older patients to all the benefits of gene therapy. We have seen the interest among our symptomatic patients and their families in gene therapy, and this study is an important step in understanding its potential to address unmet needs that remain in the SMA community.”

About STEER
STEER is a Phase 3 randomized, double-blind, sham-controlled study to evaluate the clinical efficacy, safety, and tolerability of a one-time intrathecal (IT) dose of OAV-101 in treatment naïve patients with Type 2 SMA who are between two and 18 years of age, able to sit, but have never walked. The primary objective of STEER is to evaluate the efficacy and safety of one-time IT administration of OAV-101 compared to sham controls over a 52-week period, at the end of which patients in the control arm will be treated with OAV-101. The therapeutic effect of OAV-101 will be evaluated using the Hammersmith Functional Motor Scale-Expanded (HFMSE). Secondary objectives include evaluating safety and efficacy of OAV-101 using the Revised Upper Limb Module (RULM) scale. More than 100 patients will be randomized to receive OAV-101 by IT injection or to receive a sham procedure. At the end of the 52-week period, all eligible patients who received the sham procedure will receive OAV-101 and all eligible patients who received OAV-101 will receive the sham procedure.

A sham-controlled study is a method used in clinical trials to help determine the effectiveness of a drug or treatment when a procedure is required, and has precedent in other Phase 3 studies measuring the efficacy of treatments for later-onset SMA. The use of a sham procedure in STEER is included to provide a comparison group for an unbiased collection and assessment of efficacy, safety and tolerability of OAV-101 IT for this older population where the disease progression is slower.

About Spinal Muscular Atrophy (SMA)
SMA is a rare, genetic neuromuscular disease caused by a lack of a functional *SMN1* gene, resulting in the irreversible loss of motor neurons, affecting muscle functions, including breathing, swallowing and basic movement.[1,2] The severity of SMA varies across a spectrum of types that each correspond to the copy number of the *SMN2* gene, which produces a small fraction (~10%) of functional SMN protein compared with *SMN1*.[3] Left untreated, patients with SMA Type 2 are unable to walk and will require a wheelchair, and more than 30% will die by age 25.[4] 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.[4]

About Novartis Gene Therapies
Novartis Gene Therapies is reimagining medicine to transform the lives of people living with rare genetic diseases. Utilizing cutting-edge technology, we are working to turn promising gene therapies into proven treatments, beginning with our transformative intravenous gene therapy for spinal muscular atrophy (SMA). Our robust AAV-based pipeline is advancing treatments for Rett syndrome and Friedreich’s ataxia. We are powered by the world’s largest, commercially-proven gene therapy manufacturing footprint, enabling us to bring gene therapy to patients around the world at quality and scale.

Novartis Gene Therapies 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.

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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 140 nationalities work at Novartis around the world. Find out more at https://www.novartis.com.

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