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MEDIA & INVESTOR RELEASE

New Zolgensma data demonstrate age-appropriate development when used presymptomatically and rapid, clinically meaningful efficacy in symptomatic children, even those with severe SMA at baseline

- *All children (100%) treated presymptomatically in the SPR1NT two-copy cohort survived without respiratory or nutritional support, and sat independently for ≥30 seconds, most (11/14) within the WHO window of expected normal development*
- *The majority of children (82%) treated in STR1VE-EU achieved developmental motor milestones not observed in the natural history of SMA Type 1, including patients with more severe disease*
- *More than 1,200 patients have now been treated with Zolgensma globally across clinical trials, managed access programs, and in the commercial setting*[1]

Basel, June 18, 2021 – Novartis today announced data that reinforce the transformational benefit of Zolgensma® (onasemnogene abeparvovec), an essential, one-time treatment and the only gene therapy for spinal muscular atrophy (SMA). New late-breaker data from the completed two-copy cohort of the Phase 3 SPR1NT clinical trial demonstrate age-appropriate milestone development in presymptomatic children with SMA without respiratory or nutritional support of any kind, and with no serious, treatment-related adverse events. The completed Phase 3 STR1VE-EU trial demonstrated rapid improvements in motor function following treatment with Zolgensma, and the majority of patients achieved motor milestones not observed in the natural history of SMA Type 1. Safety remained consistent with previously reported data. The data will be presented at the European Academy for Neurology (EAN) Virtual Congress 2021.

The Zolgensma data represent a significant contrast to the natural history of SMA Type 1, which leads to progressive and irreversible loss of motor function and if left untreated, often death or permanent ventilation by the age of two years.[2,3] Remarkably, all children (100 percent) treated presymptomatically in the SPR1NT two-copy cohort achieved event-free survival, were independent of respiratory and nutritional support and met the primary endpoint of sitting independently for ≥30 seconds, including 11/14 (79 percent) who achieved this milestone within the World Health Organization (WHO) window of normal development.[4] A majority of patients went on to stand independently (11/14) and walk independently (9/14), most within the typical range of normal development.[4]

Among symptomatic children with SMA Type 1 treated in the STR1VE-EU trial, including patients with more severe disease at baseline, the majority of children (82 percent) achieved developmental motor milestones not observed in the natural history of SMA Type 1, including 16 children (49 percent) who sat without support for ≥30 seconds.[5]

“With more than 1,200 children now treated, these data presented at EAN further reinforce the life-changing benefit of a one-time treatment of Zolgensma,” said Shephard Mpofu, M.D., SVP, Chief Medical Officer, Novartis Gene Therapies. “When treated with Zolgensma prior to

the onset of symptoms, not only did all patients survive, but were thriving — breathing and eating on their own and sitting independently, with many standing and walking. When you consider these newborns would go on to develop severe symptoms of SMA Type 1, a devastating, progressive disease that robs children of the ability to talk, eat, sit up and even breathe, findings from the SPR1NT trial are nothing short of extraordinary."

"STR1VE-EU included some patients with more severe SMA at baseline, yet the study demonstrated consistent and significant therapeutic benefit for symptomatic children with SMA Type 1," said Professor Eugenio Mercuri, M.D., PhD., Department of Pediatric Neurology, Catholic University, Rome, Italy. "This is a remarkable outcome that adds to the robust body of clinical evidence for Zolgensma showing that even among patients with more severe disease, Zolgensma was highly effective and demonstrated a consistent safety profile."

Final Phase 3 SPR1NT Two-Copy Cohort Results
SPR1NT is a 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 a genetic diagnosis of SMA and two or three copies of *SMN2* who were ≤6 weeks of age. Fourteen patients with two copies of *SMN2* and 15 patients with three copies of *SMN2* were treated. The majority of patients with two copies of *SMN2* develop SMA Type 1, the most common form accounting for 60 percent of cases. Data reported at EAN reflect the final data cut for SPR1NT two-copy patients. Mean age at dosing in the two-copy cohort was 20.6 days (8 – 34 days). The study of the three-copy cohort is ongoing.

Two-copy cohort (n=14) final results:

- One hundred percent of patients (14/14) met the secondary endpoint of survival without ventilatory support of any kind at 14 months of age,[4] versus only 26 percent of patients in the Pediatric Neuromuscular Clinical Research (PNCR) natural history cohort.[6]
- All patients (100 percent) achieved the primary endpoint of sitting independently for at least 30 seconds, including 11 (79 percent) who achieved this milestone within the WHO window of normal development.[4]
- Eleven patients (79 percent) could stand independently, seven of whom achieved this milestone within the WHO window of normal development.[4]
- Nine patients (64 percent) could walk independently, five of whom achieved this milestone within the WHO window of normal development.[4]
- All patients (100 percent) were independent of nutritional and respiratory support for the duration of the study.[4]
    - Nearly all patients (13/14) achieved the additional secondary efficacy endpoint of age-appropriate weight maintenance without non-oral feeding support at any visit up to 18 months of age.[4]
- All patients (100 percent) achieved or maintained a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) score of ≥58.[4] According to natural history, untreated patients with SMA Type 1 almost never achieve a CHOP INTEND score of ≥40.[6]
- All patients (100 percent) had Bayley-III fine motor performance scores similar to same-age peers without SMA and the majority (64 percent) had gross motor performance scores similar to same-age peers without SMA.[4]

All patients experienced at least one adverse event (AE) after dosing, 10 (71 percent) of which were considered to be treatment-related.[4] There were no serious, treatment-related AEs. Five patients were reported to have had serious adverse events (SAEs), all of which resolved and were not related to treatment.[4]

Final Phase 3 STR1VE-EU Results
STR1VE-EU was designed to evaluate the efficacy and safety of a single, one-time IV infusion of Zolgensma in patients with SMA Type 1 who had bi-allelic *SMN1* gene deletion or point

mutations and one or two copies of the *SMN2* backup gene, and were less than six months of age. Mean age at dosing was 4.1 months, and mean age at symptom onset was 1.6 months. The mean CHOP INTEND score at baseline was 28. All patients had two *SMN2* copies and were symptomatic with a variable degree of severity. Patients with SMA Type 1 not treated with disease-modifying therapy will never sit unassisted. If left untreated, SMA Type 1 leads to death or permanent ventilation by the age of two in the majority of cases.[2,3]

STR1VE-EU was distinct in its broadened inclusion and exclusion criteria of enrolled patients compared with START or STR1VE-US. Some patients in STR1VE-EU had a more severe disease at baseline, including lower CHOP INTEND scores and the need for nutritional and ventilatory support.[5] Of the 33 patients enrolled, nine (27%) required feeding support, an additional nine (27%) required ventilatory support and five (15%) required both at baseline.[5]

STR1VE-EU (n=33) final results:

- Thirty-three patients were enrolled; and 32 patients completed the study.
- Twenty-seven of 33 patients (82 percent) achieved developmental motor milestones not observed in the natural history of SMA Type 1.[5]
- Fourteen of 32 patients (44 percent) in the intention-to-treat (ITT) population achieved the primary endpoint of sitting independently for ≥10 seconds, observed at a median age of 15.9 months (7.7–18.6). The patient who was not in the ITT population also achieved this primary outcome measure.[5]
- Twenty-three of 30 patients (77 percent) achieved head control (three already had control at baseline), 19 of 33 (58 percent) rolled from back to sides and 16 patients (49 percent) sat without support for ≥30 seconds, including all patients who met the primary endpoint of sitting without support for ≥10 seconds.[5]
- In addition, two patients stood with assistance, and one crawled, stood, pulled to stand, and walked without assistance, all by 18 months of age.[5]
- Thirty-one of 32 patients (97 percent) achieved the secondary efficacy endpoint of survival, free from permanent ventilatory support at 14 months,[5] compared with a quarter of patients (26 percent) in the PNCR natural history cohort.[6]
- The majority of patients (73 percent) achieved a CHOP INTEND score of ≥40 points, 14 (42 percent) achieved a score of ≥50 points and three (9 percent) achieved a score of ≥58 points.[5] According to natural history, untreated patients with SMA Type 1 almost never achieve a CHOP INTEND score ≥40.[6]
- Thirteen of 33 patients (39 percent) remained independent of any type of daily ventilatory support at 18 months of age,[5] compared with none in the PNCR data set.[6]
- Of the nine patients who required ventilatory support at baseline, two achieved independence, and of the 24 patients who did not require ventilatory support at baseline, a majority of patients (67 percent) remained free from this support at the end of the study.[5]

The exploratory endpoint of the “ability to thrive” in symptomatic patients, inclusive of swallowing, feeding and age-appropriate weight maintenance, was also evaluated.[5] Twenty-three patients were in the ability to thrive population, of which seven (30 percent) met the criteria of ability to thrive at 18 months of age,[5] compared with none reported in the PNCR study.[6] Improvements in each component of the ability to thrive composite endpoint were observed. Age-appropriate weight maintenance was experienced by almost two-thirds of patients (65 percent) (greater than the third percentile for age and sex as defined by WHO guidelines) at 18 months.[5] Of the nine patients who required feeding support at baseline, four were free of feeding support at 18 months of age, and of the 23 patients in the ability to thrive population, 20 (87 percent) were fed exclusively by mouth and remained free from support at the end of the study.[5] Nine patients (39 percent) could tolerate thin liquids.[5]

As previously reported, one patient experienced a serious AE of hypoxic-ischemic brain damage and respiratory distress that resulted in death. Novartis and the investigator concluded the events and death to be unrelated to treatment with Zolgensma based on autopsy findings. Thirty-two of 33 patients were reported to have had at least one AE, of

whom six experienced 13 serious adverse events concluded by the investigator to be related to Zolgensma.[5] Reported adverse reactions in patients receiving Zolgensma were consistent with the previously described safety profile, and no new safety signals were identified.

Novartis Gene Therapies is grateful to the patients and families who take part in clinical trials, and reaffirms its commitment to using science-based innovation to improve outcomes for patients with SMA and address the unmet medical needs of SMA.

About Zolgensma® (onasemnogene abeparvovec)
Zolgensma® (onasemnogene abeparvovec) is the only gene therapy for spinal muscular atrophy (SMA) and the only SMA treatment designed to directly address the genetic root cause of the disease by replacing the function of the missing or non-working SMN gene to halt disease progression through sustained SMN protein expression with a single, one-time IV infusion. Zolgensma represents the first approved therapeutic in Novartis Gene Therapies' proprietary platform to treat rare, monogenic diseases using gene therapy. Zolgensma was approved in the U.S. in May 2019 and subsequently has been approved in 40 countries. To date, more than 1,200 patients have been treated with Zolgensma globally across clinical trials, managed access programs, and in the commercial setting.[1]

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.

About Spinal Muscular Atrophy
SMA is the leading genetic cause of infant death.[7,8] If left untreated, SMA Type 1 leads to death or the need for permanent ventilation by the age of two years in more than 90% of cases.[2,3] 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.[3,7,9] 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.[9] 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 patients with symptoms at the time of treatment will likely require some supportive respiratory, nutritional and/or musculoskeletal care to maximize functional abilities.[10] If left untreated, more than 30% of patients with SMA Type 2 will die by age 25.[10]

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 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.

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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 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 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, 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 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 110,000 people of more than 140 nationalities work at Novartis around the world. Find out more at https://www.novartis.com.

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