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MEDIA & INVESTOR RELEASE

New Zolgensma data demonstrate age-appropriate development when used early, real-world benefit in older children and durability 5+ years post-treatment

- *Children with SMA treated presymptomatically achieved age-appropriate motor milestones including sitting, standing and walking; required no ventilatory or feeding tube support; and had no serious, treatment-related adverse events*
- *Real-world data indicate older children (aged ≥6 months) achieved clinically meaningful benefit with Zolgensma alone, after or in combination with another SMA therapy, with events consistent with the previously described safety profile*
- *Zolgensma led to achievement of new milestones years after treatment in two long-term follow-up studies and resulted in sustained durability in children with SMA now up to six years old and more than five years post-treatment*
- *To date, more than 1,000 children with SMA have been treated with Zolgensma across clinical trials, managed access programs, and in the commercial setting*

Basel, March 15, 2021 – Novartis today announced new data that reinforce the transformational benefit of Zolgensma® (onasemnogene abeparvovec), an essential one-time treatment for spinal muscular atrophy (SMA). The overall safety profile remains favorable following presymptomatic treatment, in the long-term follow-up period from clinical studies and in the real-world setting. These data were presented during the 2021 Muscular Dystrophy Association (MDA) Virtual Clinical and Scientific Conference.

New data underscore the critical importance of identifying and treating SMA as early as possible. In contrast to the natural history[1] of this devastating disease, which leads to progressive and irreversible loss of motor function, children treated with Zolgensma presymptomatically in the Phase 3 SPR1NT trial achieved age-appropriate motor milestones within the World Health Organization (WHO) window of normal development – including sitting, standing and walking – were able to eat exclusively by mouth and did not require ventilatory support of any kind. There were no serious, treatment-related adverse events reported in SPR1NT. In addition, children identified via newborn screening enrolled in the RESTORE real-world registry were significantly less likely to receive more than one SMA therapy compared with those who were diagnosed clinically.

“Without the benefit of disease-modifying therapy, newborns with biallelic *SMN1* deletions and two or three copies of *SMN2* would normally develop SMA Type 1 and SMA Type 2, respectively. When treated with Zolgensma prior to the onset of symptoms, children in the SPR1NT trial achieved milestones like sitting, standing and walking at an appropriate age, grew as expected without nutritional assistance, and remained free of all forms of mechanical ventilatory support,” said Kevin Strauss, M.D., Medical Director, Clinic for Special Children in Pennsylvania. “This stands in sharp contrast to the natural progression of SMA Type 1, which would otherwise render them helpless within the first year of life and unable to

swallow, breathe, or survive without mechanical support. The transformative benefit of early intervention, as seen in SPR1NT, further underscores the urgent need for newborn screening."

Long-term follow-up data from two studies continued to demonstrate that children treated with Zolgensma experienced a sustained benefit from gene therapy in the years following dosing, with no evidence of new or delayed safety signals. Zolgensma led to achievement of new milestones years after treatment – including sitting – with sustained durability in children now up to six years old and more than five years post-treatment.

Emerging findings from the RESTORE registry – designed to provide real-world data for enhancing our understanding of patients cared for in routine practice – indicate older children (≥6 months) achieved a clinically meaningful benefit when treated with Zolgensma alone, after switching to gene therapy or in combination with another SMA therapy, with safety events consistent with the previously described safety profile. Nearly all children with two or more CHOP INTEND assessments available improved or maintained their scores, and most had a clinically meaningful ≥4-point increase.

According to Shephard Mpofu, M.D., SVP, Chief Medical Officer, Novartis Gene Therapies, "With more than 1,000 patients now treated, these data presented at MDA further reinforce what we've come to expect from Zolgensma – consistent, significant and clinically meaningful therapeutic benefit in SMA, including prolonged event-free survival, achievement of motor milestones unseen in natural history of the disease, and durability now more than five years post-dosing."

SPR1NT Data as of June 11, 2020
SPR1NT is an ongoing Phase 3, open-label, single-arm, multi-center trial designed to evaluate the efficacy and safety of a one-time IV infusion of Zolgensma in presymptomatic patients with a genetic diagnosis of SMA and two or three copies of *SMN2* who are ≤*6* weeks of age. The majority of patients with two copies of *SMN2* develop SMA Type 1, the most common form accounting for 60 percent of cases. Patients with SMA Type 1 will never sit unassisted and, when left untreated, SMA Type 1 leads to death or permanent ventilation by the age of two in the majority of cases. Most patients (>80 percent) with three copies of *SMN2* develop SMA Type 2. According to natural history, patients with SMA Type 2 never walk.

Across the two-copy and three-copy cohorts, all patients (100 percent) were alive and free of ventilatory support of any kind. All patients (100 percent) fed orally and did not require feeding tube support of any kind. According to natural history, 60 percent of two-copy patients would require feeding support by 15 months.

Two-copy cohort (n=14) findings as of June 11, 2020 data cut

- The median age of patients was 15.6 months (range 8.8–18.8 months of age).
- Eleven of 14 patients (79 percent) achieved the study's primary endpoint of sitting without support for at least 30 seconds. Ten of these patients achieved this within the WHO window of normal development. The remaining three patients were still being evaluated in the study at the time of the data cutoff.
- Five patients (36 percent) could stand independently, three of whom achieved this milestone within the WHO window of normal development. Four patients (29 percent) could walk independently, three of whom achieved this milestone within the WHO window of normal development. Of those patients who had not yet achieved these milestones, the majority (seven of 9 and seven of 10, respectively) had not yet passed the normal developmental window.
- All patients (100 percent) achieved CHOP INTEND scores of ≥50, and 13 (93 percent) achieved a CHOP INTEND score ≥58.
- All patients (100 percent) had steady gains in mean raw score of Bayley-III fine and gross motor scales.

Three-copy cohort (n=15) findings as of June 11, 2020 data cut

- The median age was 15.2 months (range 3.3–21.1 months of age).

- Eight patients (53 percent) achieved the study's primary endpoint of standing alone for at least three seconds, and six patients (40 percent) walked independently.
- These motor milestones were all achieved within the WHO window of normal development. Of those patients who had not yet achieved these milestones, all were still within the WHO window of normal development.
- All patients (100 percent) had steady gains in mean raw score of Bayley-III fine and gross motor scales.

While all patients experienced at least one AE after dosing, there were no serious, treatment-related adverse events. Seven patients were reported to have had serious adverse events (SAEs), all of which resolved and were not related to treatment.

Long-Term Follow-Up (LTFU) Studies
After the conclusion of the Phase 1 START study, 10 of 12 patients from cohort 2 (therapeutic dose) voluntarily enrolled in an ongoing observational long-term follow-up study (LT-001). As of June 11, 2020 data cut, all patients (100 percent) were alive and free of permanent ventilation. The mean age of patients was 5.2 years (range 4.7–6.1 years) and the mean time since gene therapy treatment was 5.0 years (range 4.6–5.6 years). No visits were conducted in LT-001 from December 31, 2019 through June 11, 2020. As of the December 2019 data cut, no previously achieved motor milestones were lost, and two patients (20 percent) had gained the milestone of standing with assistance (neither of whom had received treatment with nusinersen) during the follow-up period. Six patients (60 percent) did not require regular, daily respiratory support.

Patients from the completed and ongoing Phase 3 IV studies (STR1VE-US, STR1VE-EU, STR1VE-AP, SPR1NT) and the Phase 1 intrathecal study (STRONG – currently on partial clinical hold) are now enrolling in a long-term follow-up extension study (LT-002).

IV cohort (n=23) findings as of the November 12, 2020 data cut
- The mean age was 2.3 years (range 1.6–3.2 years) and the mean time since gene therapy treatment was 2.0 years (range 1.5–2.7 years).
- Eleven new milestones were achieved by four patients (17 percent), including sitting without support by all four patients (three were not receiving concomitant disease-modifying SMA therapy).
- Twenty-one patients (91 percent) were not receiving concomitant disease-modifying SMA therapy.

IT cohort (n=8) findings as of the November 12, 2020 data cut
- The mean age was 4.3 years (range 2.8–6.1 years) and the mean time since gene therapy treatment was 2.4 years (range 1.8–2.8 years).
- Four patients (50 percent) were not receiving concomitant disease-modifying SMA therapy.

In both LT-001 and LT-002, long-term follow-up does not show evidence of new or delayed safety signals, supporting a favorable benefit-risk profile.

RESTORE Registry
The RESTORE registry is an ongoing, prospective, multicenter, multinational, observational study of patients with a diagnosis of SMA, including patients from the Zolgensma managed access programs and from partnering clinical sites with a planned follow up of 15 years. The RESTORE registry provides real-world data for enhancing our understanding of patients with SMA cared for in routine practice. As of December 7, 2020, 70 patients were enrolled who had received Zolgensma when they were 6 months of age or older. Of these, 45 (64 percent) had SMA Type 1.

Real-world findings from older patients (≥6 months)
- Thirty-four patients (48.5 percent) were ≥6 to 12 months, 30 (43 percent) were ≥12 to 24 months, and six (8.5 percent) were ≥24 months of age at the time of dosing.

- 50 patients (71 percent) were on Zolgensma alone, or had switched from nusinersen and/or risdiplam.
- Of the 23 patients with two or more CHOP INTEND assessments available, 22 (nearly 96 percent) improved or maintained their score, including 15 patients with a clinically meaningful ≥4-point increase.
- Reported adverse reactions in patients receiving Zolgensma were consistent with the previously described safety profile.
- Hepatotoxicity events were reported, ranging from asymptomatic elevations in aminotransferases to acute liver failure; all resolved with prednisolone treatment. In November 2020, "Hepatotoxicity following administration of onasemnogene abeparvovec (AVXS-101) for the treatment of spinal muscular atrophy," was published in the *Journal of Hepatology*.
- Two cases of thrombotic microangiopathy (TMA) were reported as adverse events. These were both included in a series of patient case studies of TMA following treatment with Zolgensma that was published in the *Journal of Pediatrics* in November 2020.
- Two deaths have been reported: one was due to respiratory arrest assessed as unrelated to Zolgensma by both the investigator and Novartis, and one report could not be substantiated by the site investigator.

Newborn screening findings

- Twenty-eight patients were identified via newborn/prenatal screening, and 56 patients were clinically diagnosed.
- For newborn screening/prenatally identified patients compared with clinically diagnosed patients:
  - Mean age at diagnosis was 0.8 versus 3.5 months;
  - Mean age at first treatment was 1.7 versus 4.4 months; and,
  - Mean time from diagnosis to treatment was 0.9 in both groups.
- Forty (71 percent) clinically diagnosed patients received more than one SMA disease-modifying therapy compared with eight (29 percent) patients identified by newborn screening.
- Of those with two or more CHOP INTEND assessments available, 15 of 22 patients (68 percent) clinically diagnosed and eight of nine patients (89 percent) identified by newborn screening achieved clinically meaningful CHOP INTEND increases of ≥4 points between first and last assessments.

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 38 countries. To date, more than 1,000 patients have been treated with Zolgensma across clinical trials, managed access programs, and in the commercial setting[2].

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)

SMA is the leading genetic cause of infant death.[4,5] 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.[1]

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.[4] 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] More than 30% of patients with SMA Type 2 will die by age 25.[8]

About Novartis Gene Therapies
Novartis Gene Therapies (formerly AveXis) 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). This therapy is now approved in the United States, European Union, Japan, Brazil, Israel, Canada, Taiwan and Australia, and additional registrations are being pursued in close to three dozen countries, with regulatory decisions anticipated in Switzerland, Argentina and South Korea in early 2021. Our robust AAV-based pipeline is advancing treatments for Rett syndrome and Friedreich's ataxia. We are powered by the world's largest gene therapy manufacturing footprint of more than one million square feet, enabling us to bring gene therapy to patients around the world at quality and scale.

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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 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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