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MEDIA & INVESTOR RELEASE

Novartis shares Zolgensma long-term data demonstrating sustained durability up to 7.5 years post-dosing; 100% achievement of all assessed milestones in children treated prior to SMA symptom onset

- *Children in LT-001 treated after SMA symptom onset maintained or achieved additional milestones up to 7.5 years post one-time intravenous infusion*
- *All children (100%) in the presymptomatic intravenous cohort of LT-002 maintained or achieved all assessed motor milestones, including independent walking*
- *To date, more than 3,000 children with spinal muscular atrophy have been treated with Zolgensma across clinical trials, managed access programs and in the commercial setting*[1]
- *Additionally, children with SMA Type 2 treated with investigational intrathecal OAV101 maintained or achieved new development gains*

Basel, March 20, 2023 — Novartis today presented new data which underscore the transformational and sustained benefit of Zolgensma® (onasemnogene abeparvovec), an essential one-time gene therapy for the treatment of spinal muscular atrophy (SMA). Latest data from two Long-Term Follow-Up (LTFU) studies, LT-001 and LT-002, show the continued efficacy and durability of Zolgensma across a range of patient populations, with an overall benefit-risk profile that remains favorable.[2,3] These data are among a Zolgensma data set being presented during the 2023 Muscular Dystrophy Association (MDA) Clinical and Scientific Conference, which also include, in part, real-world evidence data from the RESTORE registry.

Highlighting the remarkable durability of Zolgensma, data from LT-001, an ongoing 15-year LTFU study of patients who completed the Phase 1 START study, showed that up to 7.5 years post-dosing, children who were treated after presenting symptoms of SMA maintained all previously achieved motor milestones.[2] During the time of LT-001, three additional patients also achieved the key milestone of “standing with assistance.”[2]

“I have had the privilege of observing some of the children included in the LTFU studies since they started their Zolgensma clinical trial journey, and the fact that we’re seeing them maintain and, in some cases, gain motor milestones when they are nearly eight years old is truly transformational,” said Dr. Jerry R. Mendell of Nationwide Children’s Hospital. “These children now have an improved quality of life, vastly different from what would have been expected for them if they had not received treatment. I am excited to see the new possibilities that open up to the children, their families and others who may now be able to receive this treatment.”

Interim results from the 15-year LT-002 study, which includes both presymptomatic and symptomatic patient populations, as well as intravenous (IV) and intrathecal (IT) administration methods were also presented, with all patients (100%) maintaining motor milestones achieved during their respective parent studies in the follow-up period.

Results from the IV cohort, which included 63 patients, demonstrated how a single administration of Zolgensma provided consistent, substantial and durable efficacy over time. Notably, in the presymptomatic IV cohort (n=25), all children (100%) either maintained the highest milestone achieved during the parent study (walking alone) or achieved the milestone by the data-cut off.[3] In total, six patients treated prior to SMA symptom onset and 16 treated after SMA symptom onset achieved new motor milestones in the follow-up period.

All 18 children in LT-002 who were treated with one-time investigational OAV101 IT, were alive, free from permanent ventilation and continued to show incremental gains in motor function as of the May 2022 data cut-off. Five of 16 patients who had a milestone assessment achieved new milestones during the long-term follow-up period, such as crawling, walking or standing with assistance.[3]

The majority of patients in LT-002 (70.4%, 57/81) never received add-on therapy (76.2% of the IV cohort, 50% of the investigational OAV101 IT cohort). Among patients in the intravenous cohort, 24 of 25 (96%) patients treated before symptom onset achieved the motor milestone of walking alone prior to or without add-on therapy, and 30 of 32 (93.8%) patients treated after SMA symptom onset achieved the milestone of sitting without support prior to or without add-on therapy.

“Data from the LT-001 and LT-002 studies showed that, regardless of the patient’s symptomatic status at the time of treatment, Zolgensma IV is an effective and durable treatment option. As the number of patients treated with gene therapy around the world continues to grow, our goal is that more patients, and even new SMA patient populations, will be able to experience the transformative impact of this treatment,” said Sitra Tauscher-Wisniewski, MD, Vice President Clinical Development & Analytics, Novartis Gene Therapies.

Long-Term Follow-Up (LTFU) Studies

LT-001

After the conclusion of the Phase 1 START study, 10 of 12 patients from cohort 2 (therapeutic dose) voluntarily enrolled in a 15-year ongoing observational long-term follow-up study (LT-001).[3] The mean age of enrolled patients was 7.1 years, and the mean time since administration of gene therapy treatment was 6.86 years.

Findings for the therapeutic dose cohort (n=10) as of May 23, 2022 data cut:

- All patients (100%) maintained previously achieved milestones.[2]
- All patients (100%) were alive and free of permanent ventilation.[2]
- All patients (100%) fed orally, and four (40%) did not require any feeding support.[2]
- 70% of patients did not require regular, daily ventilatory support with BiPAP more than seven years post-dosing, demonstrating a decrease in the overall use of ventilatory support.[2]
- Three patients (30%) gained the milestone of standing with assistance during the follow-up period. Two patients achieved this additional milestone without add-on therapy, and the remaining patient achieved it after the addition of nusinersen.[2]
- Four of ten patients (40%) did not receive any add-on therapy in the follow-up period. Of the six patients who did, five did not achieve a new motor milestone following add-on therapy.[2]

There were no deaths, no serious treatment-emergent adverse events (TEAEs) related to study treatment and no serious TEAEs that resulted in study discontinuation.[2] The most frequently reported events were acute respiratory failure, dehydration, and pneumonia (each in five patients, 38.5%).[2] No new safety signals were identified.[2]

LT-002

LT-002 is a voluntary Phase 4 15-year ongoing follow-up safety and efficacy study of Zolgensma IV and investigational OAV101 in patients previously treated in the Phase 3 IV studies (STR1VE-US, STR1VE-EU, STR1VE-AP, SPR1NT) and the Phase 1 IT study (STRONG).[3]

All patients, across all cohorts and parent studies, maintained previously achieved motor milestones.[3] Of the 81 patients enrolled, 77 had at least one milestone assessment.[3] In total, 48 out of 77 (62.3%) either achieved a new motor milestone in LT-002 or had already achieved all motor milestones in the parent study.[3]

IV cohort (n=63) findings as of May 23, 2022 data cut:

- Twenty-five patients (39.7%) in the IV cohort were treated prior to SMA symptom onset and 38 patients (60.3%) were treated after SMA symptom onset. The mean age of patients was 3.7 years with a mean follow-up of 3.4 years.[3]
- In the presymptomatic intravenous cohort, all four patients who did not achieve the motor milestone of “walks alone” in the parent study achieved this milestone during the follow-up period.[3]
- Additionally, motor milestones such as “crawls” and “pulls to stand” were also achieved in the presymptomatic intravenous cohort during the follow-up period, reflecting the sometimes nonlinear nature of development in children with SMA.[3]
- Thirty-two of 36 (88.9%) symptomatic patients in LT-002 achieved or maintained the milestone of “sitting without support.”[3]
- For patients with at least two assessments available, clinically significant improvement of ≥3 points in HFSME was demonstrated in 13 (81.3%) patients treated prior to SMA symptom onset and 18 (66.7%) patients treated after SMA symptom onset.[3]

IT cohort (n=18) findings as of May 23, 2022 data cut:

- The mean patient age was 5.3 years with a mean follow-up of 3.6 years.[3]
- In the follow-up period, all patients (100%) continued to show incremental gains and stability in motor function with the achievement of new motor milestones and maintenance of previously achieved milestones.[3]
- For patients with at least two assessments available, six of 12 (50%) demonstrated a clinically significant improvement of ≥3 points in HFMSE. Three patients (25%) had more than a 10-point improvement.[3]
- Five of 16 patients (31.3%) with at least one milestone assessment achieved a new motor milestone in LT-002.[3]

The majority of patients across all cohorts 57 of 81 (76% IV and 50% IT) never received add-on therapy.[3] Twenty-four patients received add-on therapy with another disease modifying treatment; of those who received add-on therapy and had at least one motor milestone assessment, half (11 of 22) did not achieve a new milestone after initiation of add-on therapy.[3]

There were no deaths and no TEAEs that resulted in study discontinuation.[3] Of the 63 patients who received OAV101 IV, 20 (31.7%) patients had at least one TEAE.[3] The most frequently reported events were gastroenteritis, nasopharyngitis, pneumonia, respiratory distress, viral infection; each reported in two patients (3.2%).[3] These events are common in children with SMA due to the underlying disease process.[3] For the 18 patients who received OAV101 IT, two (11.1%) patients had at least one TEAE. Finally, no new safety signals were identified.[3]

RESTORE Real-World Evidence

Findings from the RESTORE registry were also presented at the MDA conference, demonstrating that patients with four or more copies of the *survival motor neuron 2* (*SMN*2) gene treated with Zolgensma alone attained improvements in survival, motor function and achieved new milestones.[4] Adverse events experienced by these patients were also found to be consistent with previously reported safety findings.[4] These results continue to highlight the importance of early identification and intervention to optimize outcomes for all SMA patients.[4] 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.[4] The RESTORE registry provides real-world data to enhance the understanding of patients with SMA cared for in routine practice.[4]

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About Zolgensma

Zolgensma® (onasemnogene abeparvovec) is the only approved gene therapy for the treatment of 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 *SMN1* gene to halt disease progression through sustained SMN protein expression with a single, one-time IV infusion. Zolgensma is now approved in more than 47 countries and more than 3,000 patients have been treated with Zolgensma globally across clinical trials, managed access programs, and in the commercial setting.[1] Novartis Gene Therapies is unwavering in its commitment to reimagine the possibilities for children living with SMA and continues to evaluate Zolgensma across a robust clinical development program, as well as the investigational intrathecal administration of OAV101 in patients with later-onset forms of SMA.

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

Spinal muscular atrophy (SMA) is a rare, genetic neuromuscular disease and a leading genetic cause of infant death.[5,6] Caused by the lack of a functional *SMN1* gene, the most severe forms of SMA results in the rapid and irreversible loss of motor neurons, affecting muscle functions including breathing, swallowing and basic movement.[7] Severity varies across a spectrum of types corresponding to the number of copies of the back-up *SMN2* gene.[8] The majority (>70%) of patients with two copies of *SMN2* develop Type 1, the most common form accounting for 60% of cases.[9,10] Type 1 is severe and, left untreated, leads to death or the need for permanent ventilation by the age of two in more than 90% of cases.[5,6] Most patients (>80%) with three copies of *SMN2* develop Type 2, accounting for 30% of cases.[9] Left untreated, patients with Type 2 are unable to walk and will require a wheelchair, and more than 30% will die by age 25.[11] Loss of motor neurons cannot be reversed, so 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.[12,13]

About Novartis

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