New Drug Overview
Zolgensma (onasemnogene abeparvovec-xioi)

INTRODUCTION

- Spinal muscular atrophy (SMA) is a serious neuromuscular disease characterized by the degeneration of motor neurons, leading to progressive muscular weakness (*Bodamer 2019, Rao et al 2018*). SMA is caused by an inherited genetic mutation, and is the most common genetic cause of infant death (*Rao et al 2018*).
- SMA is an autosomal recessive inherited disorder. The overall incidence of SMA is between 4 and 10 per 100,000 live births (*Bodamer 2019*).
- SMA is usually caused by a deletion or mutation in the survival motor neuron 1 (*SMN1*) gene. The *SMN1* gene is responsible for the production of SMN protein, and mutations in the *SMN1* gene lead to a shortage of the protein. Lack of the SMN protein leads to degeneration of motor neurons, muscle weakness, and impaired movement (*Bodamer 2019, Genetics Home Reference 2019*).
  - There is also a modifying (or "backup") gene called *SMN2*, which generates a smaller amount of functional SMN protein. The number of *SMN2* gene copies varies among individuals, and patients with a higher number of *SMN2* gene copies tend to have a less severe SMA type (*Calucho et al 2018*).
- There are several forms of SMA with varying degrees of severity and ages of onset (*Bodamer 2019, Genetics Home Reference 2019, Glascock et al 2018, Markowitz et al 2012, Rao et al 2018*).
  - In SMA type 1, the most common form, untreated patients have severe weakness and hypotonia and never gain the ability to sit unsupported. Patients with SMA type 1 typically have an onset of symptoms between the age of 0 and 6 months, and have a typical lifespan of < 2 years without respiratory support.
  - Patients with SMA type 2 (intermediate), 3 (mild), or 4 (adult-onset) experience a later onset and less severe symptoms. SMA type 0 (prenatal) is the rarest and most severe form, with newborns typically living for < 6 months.
- Management of SMA has historically been limited to supportive measures (*Finkel et al 2018, Mercuri et al 2018[a]*). In 2016, the FDA approved Spinraza (nusinersen), the first disease-modifying treatment for this condition. Nusinersen is indicated for the treatment of SMA in pediatric and adult patients, and is approved for use by intrathecal injection in a series of loading doses, followed by maintenance doses every 4 months.
  - A sham-controlled trial of nusinersen (*Finkel et al 2017*) demonstrated an improvement in event-free survival and achievement of motor milestones in symptomatic patients with SMA type 1. A second sham-controlled trial (*Mercuri et al 2018[b]*) demonstrated improvement in motor function in symptomatic patients with later-onset SMA, and early results of an open-label (OL) trial (*Swoboda 2018*) demonstrated efficacy in improving motor function and milestone achievement in patients with pre-symptomatic SMA (with 2 or 3 *SMN2* copies, likely to develop SMA type 1 or 2).
- Zolgensma (onasemnogene abeparvovec-xioi; referred to as onasemnogene abeparvovec), approved by the FDA in May 2019, is the second FDA-approved product for the treatment of SMA *(FDA 2019[a]*). Onasemnogene abeparvovec was granted Priority Review by the FDA, and received Breakthrough Therapy, Fast Track, and Orphan Drug designations (*FDA 2019[a]*).
- Onasemnogene abeparvovec is a gene therapy that uses a viral vector to deliver a copy of the gene encoding the human SMN protein. The virus enters the nucleus of neurons and forms an episome (a DNA molecule that replicates independently of chromosomal DNA). The episome is transcribed and translated to produce the missing SMN protein.
- On June 28, 2019, the manufacturer of onasemnogene abeparvovec, AveXis Inc (along with its parent company, Novartis) informed the FDA about manipulation of data from animal studies, which were known prior to the product's FDA approval but not shared until after FDA approval. The FDA asserted that ensuring truthful, complete, and accurate data in product applications is a critical component of industry's responsibility, is needed to ensure the FDA is able to protect the public health, and is the law. New facility inspections were conducted by the FDA between July 24 and August 2. On August 6, the FDA published a summary of their findings. Out of the data submitted, FDA concerns were limited to a small portion of the product testing data used to support the development of the production process. The FDA felt that this information did not change the assessment of human clinical trial outcomes deemed favorable for treatment, and remained confident that onasemnogene abeparvovec should remain on the market (*FDA 2019[b,c]*).
- Medispan class: Spinal Muscular Atrophy – Gene Therapy Agents

INDICATION

- Onasemnogene abeparvovec is indicated for the treatment of pediatric patients less than 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene *(Zolgensma prescribing information 2019)*.
  - Limitations of use:
    - The safety and effectiveness of repeat administration of onasemnogene abeparvovec have not been evaluated.
    - The use of onasemnogene abeparvovec in patients with advanced SMA (eg, complete paralysis of limbs, permanent ventilator dependence) has not been evaluated.

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The safety and efficacy of onasemnogene abeparvovec were evaluated in 3 clinical trials. At the time of review, the STR1VE and SPR1NT trials (Phase 3) were unpublished and the START trial (a Phase 1, ascending-dose trial) was the only trial completed:
  - **START**: An open-label (OL), single-arm, Phase 1 trial which included 15 symptomatic patients with SMA type 1 (symptom onset ≤ 6 months of age) and 2 copies of *SMN2.* Patients were < 6 months of age at day of infusion (after protocol adjustment; the first 9 patients were required to be < 9 months of age) (mean age 6.3 months in cohort 1 and 3.4 months in cohort 2). Cohort 1 (n = 3) received a low dose and cohort 2 (n = 12) received a therapeutic dose. Published data were available through 2 years of follow-up, with additional unpublished data available through 3.9 years.
  - **STR1VE**: An OL, single-arm, Phase 3 trial which included 22 symptomatic patients with SMA type 1 with 2 copies of *SMN2*. Patients were < 6 months of age (median 3.7 months) at the time of infusion and administered a therapeutic dose. Unpublished data were available through a May 2019 cutoff date, with a mean follow-up since dosing of 12.1 months. Note: references to STR1VE in this document refer to the STR1VE trial being conducted in the United States (STR1VE-US); additional trials are ongoing in Europe (STR1VE-EU) and Asia Pacific (STR1VE-AP).
  - **SPR1NT**: An OL, single-arm, Phase 3 trial which included 18 presymptomatic patients with 2 or 3 copies of *SMN2*. Patients were ≤ 6 weeks of age (median 22.9 days) at the time of infusion and administered a therapeutic dose. Unpublished data were available through a May 2019 cutoff date (mean age 6.6 months in the 2 *SMN2*-copy cohort and 4.6 months in the 3-copy cohort).

START

- After 24 months of treatment, all patients in Cohort 2 (n = 12) were alive and none required permanent ventilation (described as ≥ 16 hours per day of required ventilatory support for 14 consecutive days in the absence of acute reversible illness or perioperative change). One patient in Cohort 1 reached a pulmonary event at 28.8 months of age awaiting salivary gland surgery, and subsequently returned below the 16 hour/day support threshold for a pulmonary event (*Mendell et al 2017, Mendell et al 2018*).
- Among the 12 patients in Cohort 2 who completed 24 months of follow-up, the following motor milestones were observed: patients were able to sit unassisted for ≥ 5 seconds (n = 11), for ≥ 10 seconds (n = 10), or for ≥ 30 seconds (n = 9). Other motor movements included achieving head control (n = 11), rolling over (n = 9), the ability to speak (n = 11), and the ability to crawl, pull to stand, stand independently, and walk independently (n = 2) (*Mendell et al 2017, Al-Zaidy et al 2019*).
  - As of April 2018, 4 patients achieved additional milestones after 24 months (including the ability to sit unassisted for ≥ 30 seconds, or the ability to stand with support [n = 2 for each]), and no previously attained milestone was lost (*Mendell et al 2018*).
- Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) is a validated scale for patients with SMA and measures motor skills using 16 items, which capture neck, trunk, proximal, and distal limb strength. The total score ranges from 0 to 64, with higher scores indicating better motor function. A 40-point threshold is considered indicative of clinically meaningful function; it is rare for infants with SMA type 1 to ever achieve this threshold. There is no minimal clinically important difference (MCID) defined in the literature; however, a 4-point change is generally considered to be important.
  - All patients in Cohorts 1 and 2 achieved increased scores from baseline on the CHOP-INTEND scale and maintained these changes during the study. In Cohort 2, the mean increase was 9.8 points at 1 month and 15.4 points at 3

months ($p < 0.001$ for both comparisons), and 11 of the 12 patients attained scores of > 40 points (*Mendell et al 2017*). In Cohort 2, at 24 months of follow-up, patients had a mean increase of 25.4 points (*Mendell et al 2018*). Scores of ≥ 40 points were achieved by 11 of 12 patients (92%), ≥ 50 points by 10 patients (83%), and ≥ 60 points by 2 patients (17%) (*Lowes et al 2018*).
  - Additional data are available for 10 patients from cohort 2 who enrolled in ongoing observational follow-up. The following results were demonstrated as of May 31, 2019 (*Avexis 2019[a]*):
    - Three of the 10 patients received concomitant treatment with nusinersen after the initial 24 months of the study.
    - In terms of survival and respiratory status, all 10 patients were alive and event-free.
    - Patients continue to maintain developmental milestones. Two patients, neither of whom have received treatment with nusinersen following onasemnogene abeparvovec infusion, gained the ability to stand with assistance. These milestones are in addition to the 2 patients previously reported who are walking independently.

STR1VE

- Early results as of the March 8, 2019 data cut-off (median duration of follow-up, 10.2 months) demonstrated the following (*Day et al 2019*):
  - Of 20 patients who reached 10.5 months of age or discontinued the study prior to 10.5 months of age, 19 (95%) were surviving without permanent ventilation. Of 15 patients who had reached 13.6 months of age or discontinued prior to 13.6 months, 13 (87%) were surviving without permanent ventilation.
    - One patient died at the age of 7.8 months due to causes unrelated to treatment, and 1 patient withdrew consent at 11.9 months of age (*Day et al 2019*).
  - The following motor milestones were observed: sitting unassisted for ≥ 30 seconds (n = 11/22; 50%), head control (n = 16/21; 76%), rolling back to side (n = 9/22; 41%), or able to crawl, pull to stand, and stand independently (n = 1/22; 5%).
  - The mean increases in CHOP-INTEND scores were 6.9 after 1 month, 11.7 after 3 months, and 14.3 after 5 months. Clinically meaningful function (or a score ≥ 40 in CHOP-INTEND) was observed in 95% of patients. Scores of ≥ 50 points were achieved by 11 of 22 patients (50%), and ≥ 60 points by 2 patients (9%).
- Additional data as of May 31, 2019 demonstrated the following (*Avexis 2019[a]*):
  - Of 22 enrolled patients, 20 were alive, without permanent ventilation, and continuing in the trial. Of 19 patients who had either reached 13.6 months of age or experienced an event, 17 patients (89.5%) survived without permanent ventilation. One patient died from respiratory failure that was determined to be unrelated to treatment, and 1 patient required permanent ventilatory support at the time of discontinuation.
  - Patients continued to gain motor milestones. Of the 6 patients who reached 18 months of age (study completion), 5 (83%) had achieved the milestone of sitting independently for 30 seconds (primary study endpoint). Additionally, 1 patient could pull to a stand and walk with assistance.

SPR1NT

- As of the March 8, 2019 cut-off date, the following results were observed:
  - All patients were alive and free of permanent ventilation.
  - Early increases in mean Bayley-III gross motor score were observed in patients with 2 *SMN2* copies, with 7 of 8 patients maintaining scores within the normal range. One patient had a score below the normal range at an age of approximately 6.5 months. Early increases in mean Bayley-III gross motor score were also observed in patients with 3 *SMN2* copies. Of the 6 patients with > 1 study visit, all maintained scores within the normal range.
  - Several patients with 2 *SMN2* copies have achieved age-appropriate motor milestones. The following motor milestones were observed: patients were able to sit unassisted for ≥ 30 seconds (n = 4/8; 50%) and stand without assistance (n = 1/8; 13%). For these motor milestones, the average age was 7.5 (range, 5.7 to 9.1) months and 8.9 months, respectively. At the data cutoff, many patients were still within or below the normal range at which motor milestones would be achieved in children without SMA.
  - The mean increases in CHOP-INTEND scores were 8.9 after 1 month and 14.4 after 3 months. CHOP-INTEND scores of ≥ 50 points were achieved by all 8 patients (100%), ≥ 60 points by 6 patients (75%), and the maximum score of 64 by 3 patients (38%) (*Strauss et al 2019*).
- Additional data as of May 31, 2019 included the following (*Avexis 2019[a]*):
  - Of the 22 patients being evaluated, all were alive and free of permanent ventilation.

- All patients with 2 copies of *SMN2* achieved or maintained a CHOP-INTEND score > 50, with 7 patients achieving a score of ≥ 60 and 5 patients reaching the maximum score of 64.
- Of patients with 2 copies of *SMN2*, 6 (60%) were able to sit without support for ≥ 30 seconds at an average age of 7.6 months. Three of these patients (30%) were able to stand with assistance at an average age of 10.1 months.

- Onasemnogene abeparvovec is still being studied in a number of trials in pursuit of expanding patient populations. The STRONG trial is a Phase 1 trial investigating intrathecal delivery in children with SMA type 2 aged 6 months to 5 years. The results from the STRONG trial will provide insights into the design of REACH, which may include patients with SMA types 1, 2, and 3 (*Clinicaltrials.gov 2019, AveXis 2019[b]*).

CLINICAL GUIDELINES

- **SMA Newborn Screening Working Group.** Treatment algorithm for infants diagnosed with SMA through newborn screening (*Glascock et al 2018*)
  - The working group was supported by CureSMA, a patient advocacy group. It brought together clinicians and geneticists with SMA expertise and patient advocacy representatives to develop a treatment algorithm for individuals who have a positive SMA newborn screening test.
  - Nusinersen was commercially available at the time of published guidance. Other approaches in development were designed to increased SMN protein levels and include a gene transfer approach using an AAV9 vector and a small molecule designed to modify *SMN2* splicing. Other products, such as potentially neuroprotective therapies, likely improve muscle function.
  - Clinical and preclinical data indicate that early treatment will be critical in order to modulate the rapid, progressive degeneration seen in SMA, particularly SMA type 1. Animal studies also show that the best results occur when drugs are given as early as possible.
  - Recommendations for the use of SMN-upregulating treatment for patients with a confirmed positive result for SMA on newborn screening are based on the number of *SMN2* copies, as follows:
    - 1 *SMN2* copy: probable SMA type 0. Treatment is recommended if the patient is truly pre-symptomatic. If symptoms are present, physician discretion is recommended. (Most patients with 1 copy of *SMN2* will be symptomatic at birth.)
    - 2 *SMN2* copies: probable SMA type 1. Treatment is recommended.
    - 3 *SMN2* copies: probable SMA type 2 or type 3. Treatment is recommended.
    - ≥ 4 *SMN2* copies: probable SMA type 3 or type 4. Waiting to treat is recommended; patients should be monitored and treated upon the onset of symptoms. (The committee was divided on this recommendation, with some participants recommending initiating treatment and other recommending patient monitoring.)
  - In patients with ≥ 4 copies of *SMN2*, who are not immediately treated with a disease-modifying therapy for SMA, the following key recommendations are made:
    - Infants identified as having ≥ 4 *SMN2* copies should be referred to someone who can identify their exact copy number (some commercial laboratories report the result only as "≥ 4").
    - Routine follow-up care should ideally occur every 3 to 6 months until the patient reaches 2 years of age, and every 6 to 12 months thereafter. This would ensure the detection of very rare cases in which children with ≥ 4 *SMN2* copies have SMA type 1 or 2.
    - Certain follow-up assessments recommended include electromyography (EMG), compound muscle action potential (CMAP), myometry, physical examinations, and motor function scales.
  - The working group acknowledges that the future availability of new FDA-approved therapies will prompt the need for additional consideration by physicians and patients, as each drug will present unique benefits, risks, and burdens.

- **SMA Care Group**. Diagnosis and management of SMA. Part 1: recommendations for diagnosis, rehabilitation, orthopedic, and nutritional care (*Mercuri et al 2018[a]*) and Part 2: pulmonary and acute care; medications, supplements, and immunizations; other organ systems; and ethics (*Finkel et al 2018*). The following recommendations outline aspects associated with supportive pharmacological care:
  - Over the last decade, the approach to treating the pulmonary manifestations of SMA has become more proactive, with introduction of therapies earlier in the disease process. Management may include airway clearance, noninvasive positive pressure ventilation, and tracheotomy ventilation in select patients. Continuous positive airway pressure (CPAP) should not be used routinely.

- Nebulized bronchodilators should be used in patients with asthma or a positive bronchodilator response.
- Nebulized mucolytics, hypertonic saline, or dornase-alpha should not be used long-term as there is no evidence to support their use.
- Glycopyrrolate should be used with caution to treat hypersalivation.
- Palivizumab should be given during respiratory syncytial virus (RSV) season as appropriate through the first 24 months of life.

○ No statistically significant effects have been demonstrated for supportive drug treatments such as creatine, phenylbutyrate, gabapentin, thyrotropin-releasing hormone, hydroxyurea, or combination therapy with valproate and acetyl-L-carnitine. Effectiveness of albuterol has not been proven, but showed functional improvement in some older, OL studies. Antibiotics, medications/supplements for bone health, and drugs for gastroesophageal reflux may be used. Influenza and pneumococcal vaccinations are recommended.

○ At the time the consensus process was completed, nusinersen was not commercially available. The guideline notes that early patient and family clinical outcomes of nusinersen have been very favorable. The guideline mentions that other approaches, such as small molecules developed to increase SMN protein level or *SMN1* gene replacement using a viral vector, have shown promising preliminary results.

SAFETY SUMMARY

- Onasemnogene abeparvovec has a boxed warning stating that acute serious liver injury and elevated aminotransferases can occur. Patients with pre-existing liver impairment may be at higher risk. Liver function should be assessed before and for at least 3 months after the infusion, and systemic corticosteroids should be administered to all patients before and after the infusion.
- Warnings and precautions include risks of thrombocytopenia and elevated troponin-I.
- The most common adverse effects were elevated aminotransferases (27.3%) and vomiting (6.8%).
- A total of 2 patients died during clinical trials: (1) a patient from the STR1VE trial, aged 7.8 months, died due to disease progression; and (2) a patient in an ongoing non-US trial was diagnosed with RSV and parainfluenza 12 days after onasemnogene abeparvovec infusion; this patient had a number of complications (ie, serious hypotension, seizures, leukoencephalopathy) and died after withdrawal of life support 52 days after the infusion.
- Where feasible, a patient's vaccination schedule should be adjusted to accommodate concomitant corticosteroid administration prior to and following onasemnogene abeparvovec infusion. Certain vaccines are contraindicated in patients on a substantially immunosuppressive steroid dose. See prescribing information for further details.

DOSING AND ADMINISTRATION

Table 1. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Zolgensma (onasemnogene abeparvovec)	Frozen suspension for infusion	IV	One time administration; 1.1 x 10^{14} vector genomes (vg)/kg	Administered over 60 minutes using a syringe pump. There are a total of 22 kit configurations, consisting of 2 to 9 vials (5.5 mL and/or 8.3 mL), to treat patients weighing 2.6 to 13.5 kg.

See the current prescribing information for full details

- Vials are shipped frozen and are stable under refrigeration for 14 days after receipt.

CONCLUSION

- SMA is a serious neuromuscular disease characterized by degeneration of motor neurons in the spinal cord and brainstem. Clinical features include progressive muscular atrophy and weakness.
  - SMA is caused by an inherited genetic mutation affecting the *SMN1* gene, causing a deficiency of the critical SMN protein.
  - Several subtypes of SMA exist, with varying severity and ages of onset.

- Onasemnogene abeparvovec is a gene therapy that uses a viral vector to deliver a copy of the gene encoding the human SMN protein.
- Onasemnogene abeparvovec is indicated for the treatment of pediatric patients < 2 years of age with SMA with bi-allelic mutations in the *SMN1* gene. Onasemnogene abeparvovec is the second approved treatment for SMA, after Spinraza (nusinersen).
- Onasemnogene abeparvovec has the potential to significantly improve the disease course of SMA with a 1-time IV dose. Published efficacy data are limited to approximately 15 patients, all of whom had SMA type 1 and 2 copies of a modifying gene, *SMN2*. Additional unpublished data provide support for use in SMA type 1 and in pre-symptomatic patients with 2 or 3 copies of *SMN2* (likely to develop SMA type 1 or 2).
  - Nusinersen has demonstrated efficacy in patients with SMA types 1, 2, and 3 and in pre-symptomatic patients; however, nusinersen requires intrathecal dosing several times per year throughout the patient's lifetime.
  - Further studies, STRONG and REACH, will also be investigating the use of onasemnogene abeparvovec when administered intrathecally for SMA types 1, 2, and 3.
- The main safety risk of onasemnogene abeparvovec includes elevated transaminases and the potential acute serious liver injury.
- Defining the place in therapy of onasemnogene abeparvovec for specific SMA patient subgroups requires additional data.

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