Dear SMA Community members,

We are delighted to be able to share with you that yesterday, the European Commission (EC) approved Zolgensma® (onasemnogene abeparvovec), a transformative gene therapy designed to address the genetic root cause of spinal muscular atrophy (SMA) by replacing the function of the missing or nonworking *SMN1* gene. Administered during a single, intravenous (IV) infusion, Zolgensma delivers a new working copy of the *SMN1* gene into a patient's cells, halting disease progression. Zolgensma does not change or become a part of the child's DNA.

Please see our press release here.

Zolgensma is the first and only gene therapy indicated for the treatment of patients with SMA. Our treatment yesterday received conditional approval from the EC, this means that the EC believe that Zolgensma addresses the unmet medical needs of patients on the basis of less comprehensive data than normally required. The available data however, indicates that the medicine's benefits outweigh its risks and that we meet the requirement to be in a position to provide the comprehensive clinical data in the future. Zolgensma is indicated in Europe for the treatment of patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1; or for patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene. The approval covers babies and young children with SMA up to 21 kg according to the approved dosing guidance.

We are so proud that with the support of SMA community members like you, we have been able to redefine the possibilities for patients and families affected by SMA with Zolgensma. Receiving this green light is a major milestone in bringing families in Europe one step closer to accessing a new treatment option, which has the potential to make a positive impact babies and small children living with SMA.

We would like to use this opportunity to thank you for your partnership, for your trust invested in us and for your continued support in bringing this treatment to the patients that need it. We intend on working hard to strengthen our relationship with the SMA community further through ongoing engaged dialogue and a truly collaborative spirit.

We are continuing our relentless pursuit to reimagine the future of rare disease treatment by applying our innovative gene therapy platform with the goal of extending treatment to all SMA patients, as well as research addressing other rare diseases. For Zolgensma, our development pipeline includes a Phase 1/2 clinical trial which is currently underway to evaluate Zolgensma's safety and efficacy for intrathecal administration in patients with SMA Type 2. This may offer an additional mode of delivery of this one-time gene therapy for older children.

At AveXis, we have worked diligently to create new pathways for access for gene therapies, a new and developing area of medicine. Recognizing that this approval will not be a solution for all families in all countries, we continue to work hard to enable access and are pursuing registration

in close to three dozen countries with regulatory decisions anticipated in Switzerland, Canada, Australia, Argentina, South Korea and Brazil in late 2020 or early 2021.

Sincerely and with thanks,

The AveXis Team

Frequently Asked Questions

1. **What is the indication and where can we find any important safety information for Zolgensma?**
    - Zolgensma is a proprietary gene therapy that provides a functional copy of the human SMN gene to halt disease progression through sustained SMN protein expression. It is administered as a single, one-time IV infusion designed to provide long-term benefit.
    - A functional copy of the human SMN gene is an adeno-associated virus (AAV) serotype 9, AAV9, which is able to cross the blood-brain barrier to the patient's neurons without modifying their existing DNA.
    - The most frequent adverse reactions (incidence ≥ 5%) observed in the 4 studies (N=44) are elevated aminotransferases 12 (27.3%) patients and vomiting 3 (6.8%) patients.
    - The final label and safety information will be distributed by the European Commission in the coming days.

2. **How many patients have been treated with Zolgensma worldwide?**
    - Over 500 patients have been treated with Zolgensma, including in clinical trials, commercially and through the Managed Access Program in the U.S.

3. **Who can receive Zolgensma in Europe?**
    - The EC granted conditional approval for Zolgensma for the treatment of patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1; or for patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene. The approval covers babies and young children with SMA up to 21 kg according to the approved dosing guidance.
        - According to Pediatric Neuromuscular Clinical Research (PNCR) natural history study of SMA, almost all patients under the age of five years of age will be under 21 kg with some patients at 6, 7 or 8 weighing below 21 kg.[1]
        - Warnings and restrictions in the label note that there is limited experience in patients 2 years of age and older or with a body weight above 13.5 kg and that the safety and efficacy of Zolgensma in these patients have not been established.
    - Ultimately, the decision to treat a child with Zolgensma should be discussed with your treating physician to determine the best treatment pathway for each specific case of SMA.

4. **Why can't patients with more than three copies of the *SMN2* gene receive Zolgensma?**
    - The EC approval was based on comprehensive data from four clinical trials including patients with one, two or three copies of the *SMN2* gene which ultimately determined the indication approved in Europe.
        - The approval was based on completed Phase 3 STR1VE-US and Phase 1 START trials that evaluated the efficacy and safety of a one-time IV infusion of Zolgensma in symptomatic SMA Type 1 patients <6 months of age at dosing, who had one or two copies of the *SMN2* backup gene, or two copies of the *SMN2* backup gene, respectively. STR1VE-EU, a comparable Phase 3 study is ongoing.

- Zolgensma demonstrated prolonged event-free survival; rapid motor function improvement, often within one month of dosing; and, sustained milestone achievement, including the ability to sit without support, a milestone never achieved in untreated Type 1 patients.[2]

  - Additional supportive data included interim results from the ongoing SPR1NT trial, a Phase 3, open-label, single-arm study of a single, one-time IV infusion of Zolgensma in pre-symptomatic patients (<6 weeks at age of dosing) genetically defined by bi-allelic deletion of *SMN1* with 2 or 3 copies of *SMN2*.
  - These data demonstrate rapid, age-appropriate major milestone gain, reinforcing the critical importance of early intervention in SMA patients.[2]

5. Is Zolgensma safe? What are the side effects?

- The most commonly observed side effects after treatment were elevated liver enzymes and vomiting.
- Acute serious liver injury and elevated aminotransferases can occur. Patients with pre-existing liver impairment may be at higher risk. Prior to infusion, physicians should assess liver function of all patients by clinical examination and laboratory testing. And, they should administer systemic corticosteroid to all patients before and after Zolgensma infusion, and then continue to monitor liver function for at least 3 months after infusion.[2]
- There is limited experience in patients 2 years of age and older or with body weight above 13.5 kg. The safety and efficacy of Zolgensma in these patients have not been established.

6. Why was Zolgensma granted a conditional marketing authorization by the EC?

- The EC granted conditional approval for Zolgensma for the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1; or for patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene.
- A conditional marketing authorization is granted in the interest of public health for medicines where the benefit of immediate availability outweighs the risk for less comprehensive data than normally required, based on the scope and criteria defined in legislation and guidelines.
  - Post-approval, we will closely monitor for any reports of related safety events in patients and encourage enrolment in the RESTORE, a global registry designed to track the effectiveness of treatments, long-term safety and overall survival global registry.
  - Conditional marketing authorizations are valid for one year and can be renewed annually.
- Once AveXis collects the necessary data to submit to the EMA, the marketing authorization may be converted into a standard marketing authorization (not subject to specific obligations).

References

1. PNCR, Pediatric Neuromuscular Clinical Research. PNCR Database: Weights (kg) by Patient Ages (Months) for SMA Types I, II, and III All Visits. Accessed March 13, 2020. WHO, World Health Organization. Growth reference 5-19 years. Weight-for-age (5-10 years). Accessed March 29, 20.
2. STR1VE-US, START and SPR1NT clinical data on file.