July 21, 2020

Dear SMA Community,

In response to your request, we are pleased to share with you information regarding the RESPOND trial, a new trial which Biogen is planning to initiate.

We understand from working with the SMA community that, despite the significant advances made in recent years, there are still unmet needs and opportunities to improve care for infants and children with SMA. Available data in the long-term study of Zolgensma (onasemnogene abeparvovec-xioi) shows that 4 out of 10 patients have moved on to treatment with nusinersen.[1,] This has also been reported in real-world experience.[2, 3,]

RESPOND Trial Overview

The RESPOND study will examine the clinical benefit and safety of nusinersen in infants and children with spinal muscular atrophy (SMA) who still have unmet clinical needs following treatment with gene therapy (onasemnogene abeparvovec-xioi). The study is projected to enroll 60 children up to age 3 who are determined by the investigator to have the potential for additional clinical improvement after receiving the gene therapy (onasemnogene abeparvovec-xioi).

The primary study group aims to include 40 infants aged 9 months or younger (at the time of first nusinersen dose) who have two copies of *SMN2* (likely to develop SMA Type 1) and received gene therapy (onasemnogene abeparvovec-xioi) at 6 months old or younger. A second study group will include 20 children and will generate data in patients with a broader age range (up to age 3 at the time of first SPINRAZA (nusinersen) dose). After a screening period, participants will receive the approved 12 mg dose of nusinersen, which is four loading doses followed by maintenance doses every four months, over the two-year study period.[4]

RESPOND is a phase 4, open-label study, so both the patient's caregiver and their physician are aware that they are being treated with nusinersen.

Efficacy assessment

People with SMA do not produce enough survival motor neuron (SMN) protein, which is critical for the maintenance of motor neurons that support sitting, walking and basic functions of life, including breathing and swallowing. The RESPOND study will seek to understand if the proven efficacy of nusinersen and its production of SMN protein may also benefit patients previously treated with gene therapy.

The efficacy of the treatment will be assessed by measuring motor function, additional patient-centred clinical outcomes (e.g. swallowing) and caregiver burden. We will also be measuring levels of neurofilament as a potential marker of disease activity (an exploratory endpoint).

Timing
The company plans to submit the study protocol to the regulatory authorities in the coming months and aims for the first eligible patients to be enrolled in the RESPOND study in Q1 2021.

Working in partnership
We recognize that there are still unmet treatment needs for people with SMA and are grateful to all the families, caregivers and investigators who continue to help us improve care for patients. The SMA community has been instrumental in helping to shape the design of this study and ensure that the clinical outcome measures being used are those that matter most to patients and their carers. The RESPOND study will help collect further data and inform treatment decisions for infants and children with SMA.

As a team we remain a dedicated, committed partner to this community and will continue to be available to provide updates in the future, when requested.

Best regards,

The Biogen SMA Team

1. Zolgensma EU Summary of Product Characteristics (SmPC). Available at: ttps://www.ema.europa.eu/en/documents/product-information/zolgensma-epar-productinformation_en.pdf. Accessed on July 13, 2020.
2. Finkel R, et al. Presented at the Muscular Dystrophy Association's (MDA) 2020 Clinical & Scientific Conference.
3. Harada Y, et al. Presented at the Muscular Dystrophy Association's (MDA) 2020 Clinical & Scientific Conference.
4. SPINRAZA U.S. Prescribing Information. Available at: https://www.spinraza.com/content/dam/commercial/specialty/spinraza/caregiver/en_us/pdf/spinrazaprescribing-information.pdf. Accessed on July 13, 2020