This material was created and funded by Biogen.

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The ASCEND Study

A clinical study in children, teenagers, and adults with later-onset Spinal Muscular Atrophy (SMA).

The ASCEND study is a global clinical trial initiated by Biogen to evaluate if patients who have previously received treatment with risdiplam, an approved SMA drug also known as Evrysdi® (risdiplam), and may not have achieved optimal clinical outcomes (e.g., improvement or delay in disease progression), may benefit from receiving a higher dose of nusinersen, also known as Spinraza® (nusinersen). People taking part in the study must have been previously treated with the maximum daily dose of risdiplam. While nusinersen is an approved drug for the treatment of SMA, the higher dose of nusinersen is not and is considered an investigational medication.

The people taking part in the study will include children, teenagers, and adults with later-onset SMA, who are unable to walk independently without support. The study will look at the motor performance in the upper limbs of these patients, as well as the potential side effects and safety concerns of the treatment. Other clinical outcomes, such as changes in health, function or quality of life will also be evaluated.

The purpose of this brochure is to share information on the study with the SMA community.

ASCEND study

For reactive use with patient organizations only.

What is SMA?

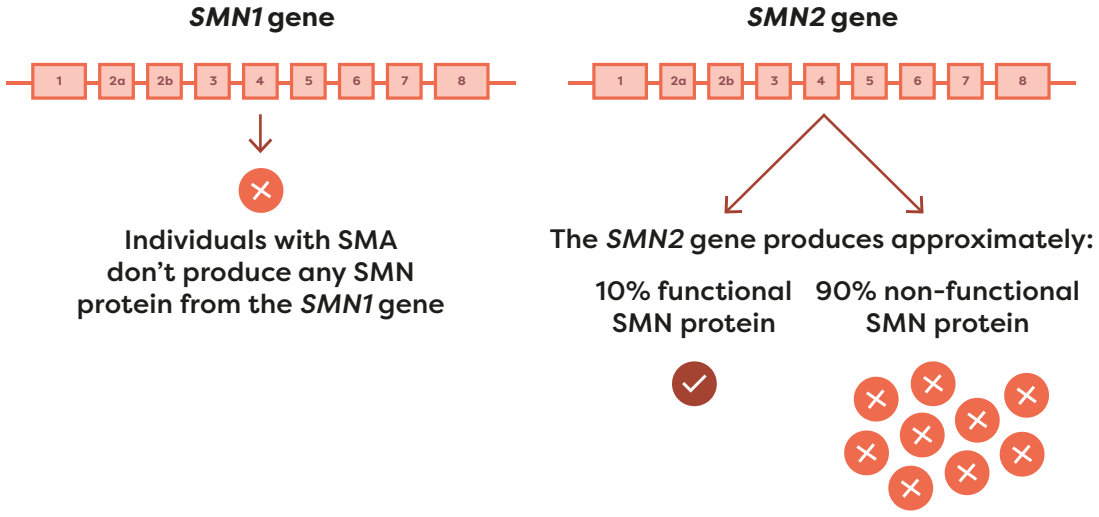
SMA is a rare, genetic disease which can lead to muscle weakness, problems with movement, and reduced life expectancy for people most severely affected.

Those affected by the most severe form of SMA (Type 1) can begin to show symptoms in the first six months of their life. The most common symptoms include limited arm and leg movement, swallowing and feeding difficulties, and breathing problems. It is also possible to be diagnosed with SMA before symptoms begin, either via a test carried out by a healthcare professional during pregnancy (called 'prenatal genetic testing'), or once the baby is born.

SMA is caused by a change in a gene called 'survival motor neuron 1 gene' *(SMN1)*. A gene is a set of instructions for making a specific protein in the body. The *SMN1* gene produces a protein called 'survival motor neuron' (SMN) protein that is important for nerve and muscle function.

Individuals living with SMA do not produce enough SMN protein. There is a 'back-up' gene called *SMN2* that produces a small amount of SMN protein. Nusinersen – a medicine approved in Europe in 2017 – works by increasing the amount of functional SMN protein coming from the *SMN2* gene. By increasing SMN protein, nerves and muscles are helped to function properly.

EXAMPLE SMN PRODUCTION FROM *SMN1* AND *SMN2* GENES IN AN INDIVIDUAL WITH SMA



What is the aim of the ASCEND study?

Clinical studies like the ASCEND study are set up to address research questions that could help inform treatment decisions, optimize the management of SMA and improve the health and wellbeing of people living with the disease. Although there are different treatment options currently available, there is still no cure for SMA, and unmet medical needs remain.

ASCEND is a global phase 3b, open-label study, which means:

- the study is not intended to acquire regulatory approval of higher dose nusinersen, but rather to provide additional information of the potential benefits
- the participant, caregiver and the doctor are aware that the participant is receiving a higher dose of nusinersen

The goal of the ASCEND study is to find out if treatment with an investigational higher dose of nusinersen has an acceptable safety profile and whether it may benefit SMA patients who have previously received the maximum daily dose of risdiplam and may not have achieved optimal clinical benefit (e.g., improvement or delay in disease progression).

Study design

Before patients can join the study, there is a screening process where tests and checks are carried out to find out if the study is suitable for them.

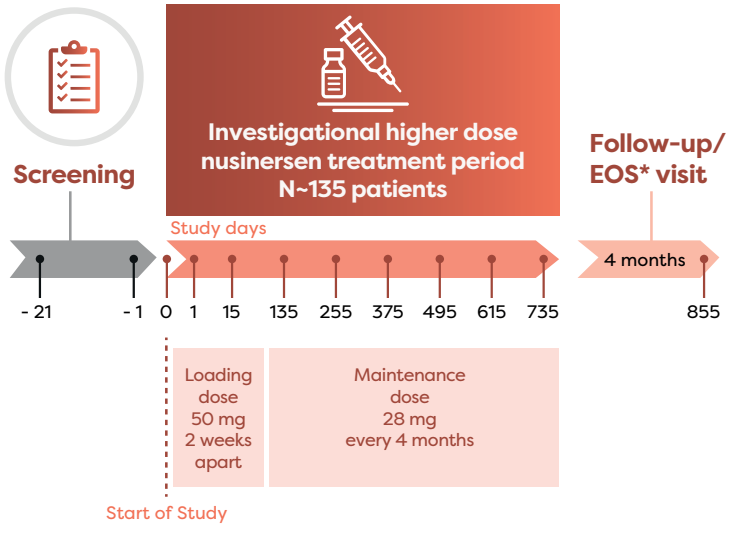
Participants in the study will receive a higher dose of nusinersen after stopping treatment with risdiplam. The total length of participation is about two and a half years and consists of a screening period, a treatment period, and an end-of-study visit. During this time participants' health will be closely monitored and assessed by a team of healthcare professionals.

Nusinersen-naive participants

- Age 5-39 years
- Risdiplam treatment for ≥ 6 months and ≤ 12 months before enrollment
- Reached the maximum daily risdiplam dose of 5 mg

Nusinersen-experienced participants

- Age 18-39 years
- Stopped nusinersen ≥ 16 months before enrollment
- Risdiplam treatment for ≥ 12 months and for ≤ 18 months before enrollment
- Reached the maximum risdiplam daily dose of 5 mg



* EOS - end of study
Participants must take their last risdiplam dose 1 day before Day 1 of the study

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Who can participate in the study?

The study plans to include up to 135 children, teenagers, and adults with later-onset SMA who have been previously treated with the maximum daily dose of risdiplam and to investigate whether there are greater health benefits from a higher dose of nusinersen. Participants will need the following criteria to be eligible:

More than **20 kg (44 lb.) body weight** and currently receiving the maximum **daily dose of 5mg risdiplam**

Agree to **stop risdiplam treatment** and switch to a **high dose of nusinersen**

SMA symptom onset at age greater than 6 months and **unable to walk 4.57 meters** (15 ft) independently without support

Must have a **Revised Upper Limb Module (RULM)** item A score of at least 3 and a RULM total score ranging from 5 to 30 at screening*

*Revised Upper Limb Module (RULM) is used to assess motor performance in the upper limbs for individuals with Spinal Muscular Atrophy (SMA) over time. Motor performance is defined as a demonstrated ability to perform 'items' that are reflective of activities of daily living. Items are performed (A through T) and a score between 0 and 37 is given. Higher scores indicate better function.

Both patients who have not received nusinersen, (nusinersen-naïve) as well as those who have previously received nusinersen, (nusinersen-experienced) will be eligible for the study based on the following criteria:

NUSINERSEN-NAÏVE

- Aged 5-39 years old
- Received risdiplam for at least 6 months, but no more than 12 months prior to enrollment

NUSINERSEN-EXPERIENCED

- Aged 18-39 years old
- Stopped nusinersen for at least 16 months prior to enrollment**
- Received risdiplam for at least 12 months, but no more than 18 months prior to enrollment

**Treatment time with risdiplam counts as time off on nusinersen

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What is being measured in the study?

During the study, healthcare professionals will assess upper limb function of the participants using the RULM, which is reflective of activities of daily living.

PATIENTS WILL BE CAREFULLY MONITORED TO SEE THE POSSIBLE EFFECTS OF A HIGHER DOSE OF NUSINERSEN ON:

- MOBILITY AND PHYSICAL ACTIVITY
- BREATHING
- SPEECH AND VOICE
- SWALLOWING/ EATING
- QUALITY OF LIFE
- VITAL SIGNS
- SIDE EFFECTS

Study locations

The ASCEND study is currently enrolling and aims to include up to 135 children, teenagers, and adults with SMA.

The study plans to enroll patients in approximately 40 different clinics worldwide. The list of locations can be found at clinicaltrials.gov (NCT05067790).

When will results be available?

Results will continue to be published over the course of the study, as well as when it is completed. These results will be shared at medical conferences and published in scientific literature, and can be made available upon specific request.

Contact details for the sponsor of the ASCEND trial:

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Clinical trial identifier numbers:

ClinicalTrials.gov Identifier: NCT05067790

Protocol code: 232SM303

EudraCT Number: 2021-001294-23

Further information can be found at:
https://clinicaltrials.gov/ct2/show/NCT05067790

www.biogen.com

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