

What is “EMBRACE?”

EMBRACE is a multi-center, Phase 2 clinical study evaluating the safety and exploratory efficacy of the investigational drug, ISIS-SMN_{Rx}, (ISIS 396443) in patients with infantile or childhood-onset Spinal Muscular Atrophy (SMA). The study is a double-blind, randomized, sham-procedure controlled study, designed to examine the safety & exploratory efficacy of ISIS-SMN_{Rx} in approximately 20 patients with SMA over a 14 month period.

What is the purpose of this study?

The purpose of the EMBRACE study is to evaluate the safety and exploratory efficacy of the drug in a small subset of patients with infantile or childhood-onset SMA who do not meet the age and other criteria of the ongoing Phase 3 studies ENDEAR & CHERISH.

Where will the study be conducted?

The study will be conducted at clinical centers in the U.S. and Europe. A listing of clinical centers participating in the study will be posted on clinicaltrials.gov (NCT02462759) as they become available.

What will the entry criteria be?

Because of the complexity of the medical criteria involved in this study, it is very important to contact a participating clinical center in order to have a full medical evaluation by expert clinical staff knowledgeable about the study. All patients who enroll in the study must meet all criteria as evaluated by a study doctor.

Guidance on the potential eligibility of children based on their age, medical assessment of symptom onset and SMN2 copy number are provided below:

- Onset of clinical signs & symptoms consistent with SMA at ≤ 6 months of age and have documentation of 3 SMN2 copies.
-OR-
- Onset of clinical signs & symptoms consistent with SMA at ≤ 6 months of age, are >7 months of age (211 days) at screening, and have documentation of 2 SMN2 copies
-OR-
- Onset of clinical signs & symptoms consistent with SMA at >6 months of age, are ≤ 18 months of age at screening, and have documentation of 2 or 3 SMN2 copies

Patients with the following medical history/status are not eligible for the study:

- Have any clinical signs or symptoms of SMA at birth or within the first week after birth
- Have a permanent tracheostomy, implanted shunt for CSF drainage, or implanted CNS catheter at screening
- Are on ventilation for ≥ 16 hours per day continuously for >21 days at screening

The following eligibility travel restrictions also apply

- Subjects with 2 SMN2 copies must reside within approximately 9 hours' ground-travel distance from a participating study site for the duration of the study.
- In addition, those residents who are >2 hours' ground-travel distance from a study site must obtain clearance from the Investigator and the study Medical Monitor

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How is ISIS-SMN_{Rx} administered?

ISIS-SMN_{Rx} is administered intrathecally. It is injected with a thin needle into a space in the lower back at the end of the spinal cord. This medical procedure is commonly referred to as a "lumbar puncture".

What does "double-blind" mean?

"Double-blind" means none of the patients, the parents or the blinded study staff will know if the patient is assigned to the drug or placebo group.

What is a "sham-procedure?"

The sham-procedure is analogous to the "placebo" group in other studies. A sham control mimics all aspects of the procedure to deliver the experimental medication with the exception of the actual delivery of the investigational drug to the patient. In the case of this study, the sham-procedure will involve a needle prick on the skin at the site of the lower back where an injection would occur. It is blinded so that patients, families and other study staff will not know whether the participant actually receives the study drug. As a result patients, families and study staff will be "blinded". This limits the possibility that the data collected in the study could be biased by any perceptions about whether or not the participant actually received the study drug. It is the best way to evaluate the effects of the drug and eliminate incidental effects of the procedure.

The use of a sham control group is a well-established and ethical practice in clinical research. The rationale for the sham procedure has been reviewed by the regulatory bodies in the countries where the study will be conducted, as well as Ethical Review Committees (also called IRBs) whose job it is to ensure the rights, safety and welfare of patients participating in studies at their institutions.

Why does there have to be a sham-procedure or placebo group in this study?

The EMBRACE study will provide data that is important to understanding the overall safety & efficacy of SMN-Rx. Therefore, consistent with the Phase 3 studies, the addition of a sham control arm in this study is necessary.

How many patients will be in the sham-procedure group?

The study will be randomized 2:1 so that two-thirds of the patients will receive ISIS-SMN_{Rx} and one-third of the patients will receive the sham-procedure. None of the patients, parents and physicians participating in the study will know whether the patients receive ISIS-SMN_{Rx} or sham-procedure.

What happens to those in sham-procedure or placebo group of the study?

All patients in the study, including those who receive the sham-procedure, will receive the same care and monitoring. Patients who complete the EMBRACE study may be eligible to participate in an open label extension ("follow on" study), provided that regulators and Ethics Committees approve the plans for the extension trial.

Are there international travel restrictions? Can I re-locate from my country in order for my child to participate in this study?

The EMBRACE study must comply with all applicable international, federal, state and local laws and regulations regarding the conduct of its clinical trials, including good clinical practices, international travel restrictions may apply. In addition, specific institutional policies regarding international patients' specific to each participating clinical center may apply. To ensure clinical study integrity, there may also be relevant ethical and practical issues to consider when enrolling pediatric SMA subjects. Additionally, patients with 2 copies of SMN2 will also need to be located within 9 hours ground travel distance from the clinical center. Finally, those residents who are >2 hours' ground-travel distance from a study site must obtain clearance from the Investigator and the study Medical Monitor

Each situation needs to be addressed on a case-by-case basis by the study doctor and their team. They may wish to talk with you about your unique family situation and may ask you to consider a variety of factors. We strongly encourage you to contact a study site to discuss your specific circumstances. It is important to have these conversations BEFORE you make any decisions for you or your family.

| What if my child does not qualify for this study?

We are focused on executing the clinical studies in the SMN_{Rx} program, which includes the ENDEAR, CHERISH, NURTURE & EMBRACE studies, in order to appropriately test this investigational drug and pursue potential regulatory filings as quickly as possible. It is equally important that we recognize the contribution of those participating in sham controlled clinical trials, who participate with the understanding that the only benefit they may receive is advancing the scientific knowledge of SMA research. For these reasons, there are currently no plans to provide access outside of the current clinical studies.

Are you not studying my type because you don't think the drug will work for me?

At this time, the safety and effectiveness of ISIS-SMN_{RX} is not yet proven in any population. The pivotal studies in the clinical program have been designed with the intent of robust evaluation of the safety and efficacy of the drug in as short a time frame as possible.

Where can I go for further information about SMA?

The website www.LearnAboutSMA.org has some excellent information about SMA. Other good resources are www.curesma.org, www.smafoundation.org, and www.mda.org.

Where can I get more information about this study?

A summary list of eligibility criteria for this trial can be found at www.clinicaltrials.gov (NCT02462759). Given the complexity of the criteria we strongly suggest that interested families contact a participating clinical center for more detailed discussion.

Where can I go for further information about Clinical Trials?

There are many excellent resources to learn more about clinical studies/clinical research, notably:

<https://www.clinicaltrials.gov/ct2/about-studies>

For more information about the ISIS-SMN_{RX} Clinical Studies:

www.ClinicalTrials.gov

- ENDEAR (NCT02193074)
- CHERISH (NCT02292537)
- NURTURE (NCT02386553)
- EMBRACE (NCT02462759)