

Frequently Asked Questions – CALLISTO Phase 1 Clinical Trial

What is CALLISTO?

- CALLISTO is a phase 1, ascending multiple dose cohort trial to establish the pharmacokinetic profile of omigapil in paediatric and adolescent patients with CMD and to evaluate the safety and tolerability of omigapil.

Who funded the trial?

- The study sponsor is Santhera Pharmaceuticals. Significant additional funding was provided by Cure CMD; the Swiss Foundation for Research on Muscle Diseases (FRSMM); EndoStem, an EU 7th Framework program; and, a FDA Orphan Products Development grant. Moreover, the NIH contributed significantly by conducting this study.

What is omigapil?

- Omigapil is a small molecule, an oral drug, which was first discovered and clinically developed by Novartis. Santhera licensed omigapil to study for development in congenital muscular dystrophy.

How does omigapil work?

- Omigapil's proposed mechanism of action is anti-apoptosis, meaning it prevents cell death. Studies in a mouse model of the MDC1A type of congenital muscular dystrophy have shown that omigapil inhibits cell death and reduces body weight loss and skeletal deformation, while increasing locomotive activity and protecting from early mortality. There is some data suggesting this is the case in Collagen VI CMD as well.

Will omigapil only being further developed in the Collagen VI- and MDC1A-subforms of CMD?

- Collagen VI and MDC1A subforms of congenital muscular dystrophy have the strongest evidence to support that apoptosis (or programmed cell death) occurs in the disease and that a drug with anti-apoptotic properties could help treat the disease.

How is omigapil delivered?

- The omigapil drug substance is a white, micronized powder. For clinical administration, it is used as a liquid formulation orally. The liquid form of omigapil offers flexible dosing, and can be tolerated by patients with swallowing difficulties or used in g-tubes.

What is a Phase 1 trial?

- A phase 1 trial is a smaller trial, typically enrolling 20-100 healthy volunteers or people with the disease with the purpose of studying pharmacokinetics and safety/tolerability. Phase 1 studies are closely monitored and gather information about what the body does with the drug (absorption, distribution, metabolism, excretion), how much of a drug the body can tolerate and what the side effects of a drug are. Early information about how to best administer the drug to limit risks and maximize possible benefits also can be obtained. Omigapil had already been investigated previously in healthy volunteers but additional information needed to be gathered in children and adolescents, using a liquid formulation, and in the CMD patient population. The study protocol of the CALLISTO trial had been reviewed and was agreed with the US FDA.

What does pharmacokinetic mean?

- A pharmacokinetic study examines how a drug moves through the body. The time it takes for a drug to be absorbed, distributed, metabolized, and excreted is studied and amounts of active and metabolized drug are quantified. This type of study is necessary to develop safe and effective therapies and identify a suitable formulation and dose. We had to conduct this study because it was not known how this formulation acted in the body of children and adolescent with CMD. Omigapil was previously studied using tablets in an adult population.

Why was there only one study site (in the U.S.)?

- The NIH under the leadership of Dr. Bönnemann and Dr. Foley and their team was well-positioned to undertake the first investigative drug trial in this disease. Further clinical studies will be conducted in several countries in Europe and the US.

Who was eligible to participate in this study and how were patients chosen?

- Ambulatory and non-ambulatory children ages 5-16 years with clinical picture consistent with collagen VI-deficient (Ullrich) or laminin alpha-2 (merosin) deficient (MDC1A) CMD were eligible to participate in the trial. Participants were on stable doses of any allowed concomitant medications for one month prior to dosing.
 - Exclusion Criteria:
 - Recurrent hospitalisation for chest infections in previous 2 years
 - Patients with respiratory function parameters (eg: low pulmonary function test value) currently affected by short term medications, or acute illness/ conditions
 - Any need for surgery (scoliosis, gastrostomy, other) 6 months prior to the study or planned during the course of the study
 - Weight less than 17kg at Baseline
 - Morbidly obese or grossly overweight
 - History of epilepsy or on antiepileptic medication at Screening/Baseline
 - Diabetes
 - On daytime non-invasive Ventilation (NIV)
 - Anticipated need for anesthesia during the course of this study
 - Patients with renal impairment or with moderate to severe hepatic impairment
- Cure CMD, MDA and the NIH advertised the trial and Cure CMD reached out specifically to patients who might qualify.

Did the trial participants experience any notable gains in strength?

- Because this is a phase 1 trial focused on dosing and safety, we don't anticipate seeing any changes in the strength of patients over the three months they were on omigapil. The number of patients and the duration of the trial was too small to expect any measurable clinical effect. However, we will continue to analyse the data from the study and share those with the CMD community.

Will omigapil make my child stronger?

- We hope to examine the efficacy of omigapil in a future trial, but this trial was focused on safety, pharmacokinetic profile and dosing. We have no data yet on the efficacy of omigapil.
- Will omigapil cure CMD? No, we do not anticipate omigapil to be a complete "cure" as most people think of it. We do hope that omigapil will be shown to positively impact the symptoms, muscle weakness, muscle breakdown and mortality associated with CMD, but future studies are needed to determine that.

Are there any harmful effects from taking omigapil?

- There were no safety concerns during the trial. The Drug Safety Monitoring Board concluded that omigapil was safe and well tolerated in the paediatric and adolescent population of CMD patients enrolled in CALLISTO.

How long did the trial take to conduct?

- As this was a trial requiring a step-wise change of the dose and included very intense monitoring of the patients, it took almost two and a half years to complete. The first patient was dosed in July of 2015 and the last visit of the last patient in the trial was in January of 2018.

When will the full results be released?

- We will be taking the next months to fully analyse the trial data. The investigators of the NIH will release the findings at upcoming scientific meetings. At that time, we will hold a webinar for the CMD community to share these results and answer questions.

Now that the trial is over, does it mean that omigapil is now available for me/my child to take?

- Omigapil is still an investigational drug and is not available by prescription. There are studies that still need to take place in addition to discussions with the regulatory authorities prior to omigapil being approved.

What is a phase 2 trial?

- A phase 2 trial traditionally follows a phase 1 trial. The drug would be administered to a larger number of patients with the goal of studying efficacy (benefits) and side effects of the drug. In rare diseases such as CMD, a phase 2 trial could be suitable as pivotal trial supporting an approval. We will discuss this option with regulators in the US and Europe.

Are there plans for a Phase 2 trial? What conditions must be met before this can be decided?

- Prior to planning a phase 2 trial, we must fully analyse the results of the phase 1 study, determine that we have reliable endpoints for a future trial, and talk with regulators about the best development path to approval.
- We also will assemble a scientific advisory group of leading experts in the CMD field to discuss how to best move forward with the development of omigapil for CMD.
- When will these advisors meet? We plan to have such a first meeting during summer 2018.

Will there be multiple sites in a Phase 2 trial?

- Yes, in the case of a phase 2 trial we would have multiple study sites.

How do we volunteer to participate in a Phase 2 trial?

- We aren't at that point yet. The best thing families can do is make sure their information is entered and up-to-date in the Cure CMD patient registry. The Cure CMD registry proved a vital resource for us to fully recruit this study.

What can we do to ensure a Phase 2 trial happens (advocacy, fundraising, etc.)?

- We are working with experts and advocacy groups to move omigapil forward in the most expeditious way possible.

When will you know what the next steps are and the timeline to start the next trial?

- We will be able to better inform the community about the next steps and our timeline near the end of 2018.

How long will it be until omigapil comes to market and is available to patients?

- There are additional trials to take place before then and it is premature to speculate on timelines at this point.

How much will omigapil cost?

- There is a significant amount of work that needs to take place before thinking about the price of a drug. We need to establish the efficacy of the drug, conduct additional trials, meet with advisors, and meet with regulatory authorities. At this stage we have no guidance on future pricing.

What is an orphan drug?

- Omigapil has orphan drug designation in the United States and Europe. This is awarded to investigational drug candidates aimed to treat rare diseases.

What is Fast Track Designation?

- Omigapil has Fast Track Designation in the United States from the FDA. Fast track is a process designed to expedite the development and review of drugs to treat a serious condition and fill an unmet medical need.
- Fast Track Designation affords the company developing the drug more frequent communication from the FDA, eligibility for an Accelerated Approval and Priority Review if certain criteria are met, and a rolling review (completing sections of the application and submitting them for review rather than wait until the entire application is completed for the review to begin).

Who can I contact for additional information?

- Please contact Santhera's Head of Patient Advocacy for the U.S., Jodi Wolff, at Jodi.wolff@santhera.com or the Head of Patient Advocacy for Europe, Vanessa dos Reis Ferreira at vanessa.dosreisferreira@santhera.com . We are happy to answer any questions that you have about the trial and next steps.