

Congenital Muscular Dystrophy Ascending Multiple Dose Cohort Study anaLyzing Pharmacokinetics at three dose Levels In Children and Adolescents with Assessment of Safety and Tolerability of Omigapil (CALLISTO)



National Institute of Neurological Disorders and Stroke
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Clinical Research Protocol

Abbreviated Title: CALLISTO
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Date of This Submission/Version (*see header*)
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Eudract Number: 2012-002700-40
Compound: Omigapil Hydrogen Maleate
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Synopsis

Study Title	Congenital Muscular Dystrophy Ascending Multiple Dose Cohort Study analyzing Pharmacokinetics at three dose Levels In Children and Adolescents with Assessment of Safety and Tolerability of Omigapil
Study Number	SNT-I-015
Study Phase	1
Study Acronym	CALLISTO
Planned Study Duration	84 weeks (16 weeks recruitment, 68 weeks study conduct). The above duration is assuming cohorts are dosed in staggered parallel. Patient participation will be up to 28 weeks (up to 4 weeks screening, 4 weeks run-in, 12 weeks treatment and a follow-up visit 8 weeks post last dose taken)
Investigational Product Dosage and Route of Administration	Omigapil oral solution (0.1 and 0.25 mg/ml in Humco [®] Cherry Syrup) Dosage: 0.02, 0.08 and 0.2 mg/kg/day; maximum daily dose: 5 mg Oral administration once per day after breakfast
Vehicle	Humco [®] Cherry Syrup
Indication	Congenital Muscular Dystrophy (CMD)
Study Objectives	<ul style="list-style-type: none">• The primary objective is to establish the pharmacokinetic profile of omigapil at a range of doses in pediatric and adolescent patients with CMD• The secondary objective is to evaluate the safety and tolerability of omigapil at a range of doses in pediatric and adolescent patients• The tertiary objective is to establish the feasibility of conducting disease-relevant clinical assessments in pediatric and adolescent patients with CMD to aid in the design of future studies
Study Endpoints	<ul style="list-style-type: none">• The Primary Endpoint is the pharmacokinetic profile of omigapil and metabolites quantified by C_{max}, C_{min}, t_{max}, $t_{1/2}$, AUC_{0-t}, AUC_{0-8h}, AUC_{0-24h}, λ_z (terminal phase rate constant) and R_o (the extent of accumulation in plasma)• The Secondary Endpoint is safety and tolerability of omigapil at the doses tested, established through the collection of Adverse Events (AEs) and Serious Adverse Events (SAEs), vital signs, oxygen saturation, standard lab parameters and electrocardiogram (ECG) assessments.• The Tertiary Endpoint is the outcome of disease-relevant clinical assessments.<ul style="list-style-type: none">• Hospital-based pulmonary function tests (PFTs) by standard spirometry.• Home-based pulmonary function tests using a child-compatible hand-held device (ASMA-1).• Hospital-based evaluation of muscle strength & function.• Motor function scales.

- Time tests (ambulatory patients only).
- Functional Scales.
- Muscle Imaging (Muscle magnetic resonance imaging (MRI) and Muscle Ultrasound)
- Collection of biomarkers

Number of Centers

1

Number of Subjects
Patient Population

Approximately 20 eligible patients will be randomly assigned to ensure a minimum of 16 patients who have completed all study procedures (3 cohorts of 4, 4, and 8-12 patients)

Inclusion Criteria

- Ambulatory and non-ambulatory patients from age 5 - 16 years (≥ 5 years old and < 17 years old) at time of screening with a clinical picture (see below) consistent with COL6-related dystrophy (COL6-RD) or LAMA2-related dystrophy (LAMA2-RD)
- Under regular review at a neuromuscular center
- On adequate double-barrier contraception (if of child-bearing potential (CBP))
- Stable on any allowed concomitant medications for 1 month prior to run in phase
- Forced Vital Capacity (FVC) 30-80% of the predicted value and confirmed at Screening and Baseline visit(s)

For patients with Collagen VI-related dystrophy (COL6-RD)– required clinical picture

- Muscle weakness: inability to walk or, if patient is still ambulatory, inability to run and > 5 s for 10 m walk

Genetics and Pathology:

- Molecular diagnosis of COL6-RD, defined by one dominant or two recessive mutation(s) in COL6A1, COL6A2 or COL6A3 known to cause the clinical picture,
OR
- Histological diagnosis showing (i) absent or significantly decreased expression of collagen VI in muscle (overall reduction or basal lamina specific) or (ii) absent or significantly abnormal matrix in skin fibroblast culture

For patients with Laminin alpha 2 related dystrophy (LAMA2-RD) – required clinical picture

- Muscle weakness: Inability to walk; if patient is still ambulatory, inability to run and > 5 s for 10 m walk.

Genetics and Pathology:

- Either: 2 identified pathologic or probable pathologic mutations in LAMA2 gene
OR
- 1 identified pathologic or probable pathologic mutation in LAMA 2 gene with evidence of decrease in laminin alpha 2 staining on muscle or skin biopsy

OR

- Evidence of decrease in laminin alpha 2 staining on muscle or skin biopsy with matching clinical phenotype and no suspicion of alpha dystroglycanopathy (aDG-RD) (clinically or by staining on muscle biopsy)

Exclusion Criteria

- Use of any investigational drug other than the study medication within 12 weeks of study start.
- Recurrent hospitalization for chest infections in previous 2 years (≥ 2 per year)
- Patients with respiratory parameters (eg: low pulmonary function test value i.e. $<30\%$ predicted or need for daytime non-invasive ventilation) currently affected by short term medications, or acute illness/ conditions (conduct baseline assessments when the patient has recovered and is no longer taking acute medication)
- Any need for surgery (i.e. scoliosis, gastrostomy, other) in the preceding 24 weeks or foreseen during the course of the study.
- Patient has an intercurrent significant medical condition or situation which in the opinion of the Investigator or the study Medical Monitor may put the patient at significant risk, confound the study results or interfere significantly with the patient's participation in the study.
- Failure to thrive, defined as:
 - Falling 20 percentiles (20/100) in body weight in the 12 weeks preceding Screening/Baseline (based on family report of weight loss and review of relevant medical records)
 - In patients below the 3rd percentile, any further drop in body weight percentile in the 12 weeks preceding Screening/Baseline (based on family report of weight loss and review of relevant medical records)
- Weight less than 17 kg at Baseline
- Morbidly obese or grossly overweight (≥ 86 percentile body mass index (BMI) in children)
- History of epilepsy or on antiepileptic medication at Screening/Baseline
- Diabetes
- On daytime Non Invasive Ventilation (NIV)
- Intake of prohibited medication (as listed in Appendix I)
- Anticipated need for anesthesia during the course of this study
- Patients with renal impairment defined as urinary protein concentration ≥ 0.2 g/L
- Patients with moderate to severe hepatic impairment.
 - ALT $\geq 8x$ upper limit of normal (ULN) and total bilirubin $2x$ ULN (plus $>35\%$ 'direct' bilirubin), or
 - ALT $\geq 8x$ ULN and INR >1.5 or ALT $>2x$ baseline levels, and total bilirubin $> 2x$ ULN (plus $>35\%$ 'direct' bilirubin),
 - or
 - ALT $>2x$ baseline levels, and INR greater than 1.5,

	<ul style="list-style-type: none">• or• ALT ≥ 8 x ULN and associated with symptoms of hepatitis (e.g. onset or worsening of nausea, anorexia, jaundice or abdominal pain) or hypersensitivity (e.g. fever, rash, eosinophilia),• or• GGT > 2-3x ULN and bilirubin 2x ULN (plus >35% 'direct' bilirubin) or• GGT >2-3x ULN and INR >1.5
Participation Period	28 weeks per patient – up to 4 weeks screening, 4 weeks vehicle (Humco® Cherry Syrup) run-in phase followed by 12 weeks on omigapil and a follow-up visit 8 weeks after last dose.
Study Design	<p>This study will be an open-label, sequential group, ascending oral dose, continual reassessment method (CRM) based model, pharmacokinetic, cohort study.</p> <p>A Data and Safety Monitoring Board (DSMB) will be established to monitor patient safety throughout the study.</p>
Pharmacokinetics	<p>Pharmacokinetic (PK) parameters of omigapil and metabolites, such as C_{max}, C_{min}, t_{max}, $t_{1/2}$, AUC_{0-t}, AUC_{0-8h}, AUC_{0-24h}^*, λ_z and R_o (*if sufficient data are available) will be calculated.</p> <ul style="list-style-type: none">• During the first 8 hours following initial intake of the study medication (Visit 2) <p>and</p> <ul style="list-style-type: none">• After 4 weeks of daily dosing, during 8 hours following study medication intake (Visit 3) <p>and</p> <ul style="list-style-type: none">• After 12 weeks of daily dosing, during 8 hours following study medication intake (Visit 5)• On each occasion, 7 blood samples (1 pre-dose and 6 post-dose time points at 0.5, 1, 1.5, 2, 4, and 8 hours) will be collected; (3 ml per sample; 21 ml per visit).
Safety Evaluations	<ul style="list-style-type: none">• Physical examination, vital signs including body temperature, ECG, pulse oximetry, laboratory assessments such as complete blood cell counts (CBC), comprehensive metabolic panel (CMP), liver ultrasound, urine analysis and AE collection
Efficacy Evaluations	<p>Feasibility</p> <ul style="list-style-type: none">• Hospital-based pulmonary function tests by standard spirometry: Forced Vital Capacity (FVC), Slow Vital Capacity (SVC), Forced Expiratory Volume (FEV1), Peak Expiratory Flow (PEF), Maximum Inspiratory Mouth Pressures (MIP), Maximum Expiratory Mouth Pressures (MEP), Peak Cough Flow (PCF) and Sniff Nasal Inspiratory Pressure (SNIP).• Home-based pulmonary function tests using a child-compatible hand-held device (ASMA-1): PEF and FEV1• Hospital-based hand-held myometry: elbow flexion, elbow extension, knee flexion, knee extension, myotools/Moviplate

- Hospital-based goniometry: knee extension/flexion contracture, elbow flexion contracture, ankle dorsiflexion
- Hospital-based Timed tests: 2 minute walk and 10 meter walk
- Hospital-based motor function scales: North Star, MFM 32, Performance Upper Limb (PUL) scale, Jebsen Hand Function Test
- Hospital-based functional Tests: ACTIVLIM, Egen Klassifikation (EK2)
- Muscle imaging (muscle ultrasound and muscle MRI)

Study Procedures

16-20 CMD patients (8-10 COL6-RD and 8-10 LAMA2-RD) whose weight, age, and FVC likely meet the inclusion/exclusion criteria will be notified of the study. Patients may be identified using known data from the annual Congenital Muscular Dystrophy natural history study (CMD Comparative Outcome Measure Study- CMD COM) at the NIH or through the CMDIR. Trial flyers will be distributed through an outreach organization Cure CMD as well as through other community contacts. Patients who have learned of the trial by any means, including clinicaltrials.gov and flyer distribution, may contact the investigators directly and be considered for screening.

A pre-screening call will be scheduled to confirm interest to participate and to give verbal assent for release of medical records data within the NIH in order to confirm eligibility. Preliminary determination of eligibility at the pre-screening evaluation will include: patient age, patient disease type, current weight in kilograms, recent hospitalization history, any known/ planned upcoming surgical interventions, pulmonary function test data (specifically forced vital capacity), medical history (list of current additional known medical diagnoses), and list of current medications. Upon identifying a confirmed cohort of at least 8-10 COL6-RD and 8-10 LAMA2-RD patients, each patient will be assigned a de-identified number.

Two participant variables: CMD subtype and current weight (in kilograms) will be sent to the RAE. Patients will be stratified by disease type and weight and will be similarly represented. For each strata, one patient will be assigned from each strata to each dose-escalating group (cohort), so that the cohorts will have similar representation of disease type and weight, to ensure comparable PK, safety, tolerability and efficacy feasibility assessment data. In the event of a patient drop out, study investigators will replace the patient with another from the same stratum. Patients who discontinue study drug or express intent to withdraw will be asked to return for a final safety follow-up visit prior to withdrawal. Furthermore, patients who are withdrawn due to safety reasons (e.g. AE, SAE) will be followed up with safety calls and may be requested to return for study visits for safety assessments to be performed as necessary. Thus, using this procedure, approximately 20 CMD patients will be assigned to one of three dose-escalating cohorts

of 4 patients, 4 patients, and 8-12 patients in order to obtain a total of 16 to 20 patients completing the study. Each cohort will receive one of three doses of omigapil daily for 12 weeks.

Patients will have the possibility to perform the screening and baseline visits combined or within a period of less than 6 days in order to allow for the laboratory results to be available to confirm patient eligibility. Up to 7 study visits will be required: Screening; Visit 1 - Baseline/initiation of run-in phase; Visit 2 - Week 4/ initiation of omigapil dosing; Visit 3 - Week 8 after 4 weeks of omigapil dosing; Visit 4 – Week 12 after 8 weeks of active treatment; Visit 5 – Week 16 after 12 weeks of omigapil dosing; Visit 6 – Week 24, Follow-Up visit, 8 weeks after stopping the drug.

Patient management will be the same for all three Cohorts.

- At Screening, which should take place no more than 4 weeks prior to Baseline/Visit 1, written informed consent/assent will be obtained and the eligibility of the patient will be assessed. For further details on procedures that will be done at this visit, see Section 4.3.3.
- At Visit 1/ Baseline (or Screening/Baseline if the visits are combined or within 6 days of each other to allow for all information to confirm eligibility to be available such as laboratory results) patients will undergo the safety evaluations and efficacy feasibility assessment tests if the patient is capable of performing them. Patients will be dispensed a 4-weeks supply of vehicle (Humco® Cherry Syrup) and given an appointment for Visit 2 (Day 1 of omigapil dosing). AEs will be collected during this run-in period for comparative purposes. To assist with AE capture and dosing compliance, patients and/or their caregivers will be asked to maintain a diary card (See Appendix H) throughout the study period. This will be reviewed at each visit. For further details on procedures that will be done at this visit, see Section 4.3.4.
- At Visit 2/ Week 4, patients will repeat the safety evaluations. The first dose of omigapil will be given during this visit and PK sampling will also be initiated.
 - Blood samples for PK will be taken pre-dose and at 0.5, 1, 1.5, 2, 4, and 8 hours post-dose.
 - Vital signs and oxygen saturation using a pulse oximeter will be monitored throughout the day and patients monitored for treatment emergent adverse events.
 - Patients will be dispensed sufficient omigapil for 4 weeks of omigapil dosing.
- Interim Calls: A safety follow-up call will be made in weeks 5, 6 and 7 (after approximately 1, 2 and 3 weeks of starting omigapil dosing) to elicit reporting of any treatment emergent adverse events.

- At Visit 3/ Week 8 (after 4 weeks of omigapil dosing) an identical visit to Visit 2 with safety assessments and full PK sampling will be performed.
- Interim Calls: A safety follow-up call will be made in weeks 9, 10 and 11 (after approximately 5, 6 and 7 weeks of starting omigapil dosing) to elicit reporting of any treatment emergent adverse events.
- DSMB Review:
 - After the first patient of each cohort has completed Visit 2, the PK samples collected at visit 2 will be sent to the laboratory for analysis. At that point, all available data from the PK analysis, safety and tolerability for the first patient of each cohort will be provided to the DSMB to ensure that the PK data reflects the expected PK profile and no major safety concerns are detected. The DSMB will make a recommendation on the continuation of the cohort at the planned dose.
 - Thereafter, as soon as the last patient in the cohort has had their Visit 3, the site will send all PK blood samples from all the patients dosed to the laboratory for analysis.
 - Data from the PK analyses, safety and tolerability from Baseline to Visit 3 will be provided to the DSMB for review once all necessary data is available. Based on this review the DSMB will make a recommendation (including any dose adjustments) on the initiation of the next cohort.
 - At subsequent meetings, the DSMB will be provided with all safety data from the completed and on-going cohort(s) in addition to PK data from the cohort under review. Patients in the cohort under review will continue their treatment uninterrupted during DSMB review unless Stopping Rules are invoked.
- At Visit 4/ Week 12 Safety evaluations and efficacy feasibility assessments (as capable) will be conducted. PK sampling will not be done.
- Interim Calls: A safety follow-up call will be made in weeks 13, 14 and 15 (after approximately 9, 10 and 11 weeks of starting omigapil dosing) to elicit reporting of any treatment emergent adverse events.
- At Visit 5/ Week 16 the patient will attend a half day hospital visit to do efficacy feasibility assessments (as capable) before returning to the clinic the next morning to do PK sampling as described for Visit 2.
- In Week 20 (approximately 4 weeks post omigapil dosing) the site will make a safety follow-up call.
- At Visit 6/ Week 24 (8 weeks after study drug discontinuation) the patient will attend a final visit to the site (Visit 6) for a safety evaluation and efficacy feasibility assessment testing (as capable).

Random Assignment Method This is an open-label, sequential group, ascending, multiple dose study in which Cohort 1 will complete at least the first 4 weeks of active treatment before Cohort 2 can be initiated; and in which Cohort 2 will complete the first 4 weeks of active treatment before Cohort 3 can be initiated. Stratification methodology will be described in the Random Assignment Specification Guidelines. A random assignment expert (RAE) will be designated to perform the random assignment and will be trained on the Random Assignment Guidelines. The RAE will hold a master's degree in statistics or be a pharmacist.

In order to avoid possibility of bias being introduced whereby the patient demographics will not be similar across cohorts, random assignment of patients to 3 cohorts will take place once a minimum of 8-10 patients with COL6-RD and 8-10 patients with LAMA2-RD have been successfully pre-screened, have confirmed interest and intent to participate. Using the random assignment method, the entire group will be randomly assigned by the RAE to Cohorts 1, 2 and 3 after stratification using 2 patient variables: CMD subtype (COL6 or LAMA2) and current weight (kilograms). For each strata, the RAE will randomly assign one patient from each strata to each dose-escalating group (cohort), so that the cohorts will have similar representation of disease type and weight, to ensure comparable PK, safety, tolerability, and efficacy feasibility assessment data. Thus, using this procedure, approximately 20 CMD patients will be assigned to one of three dose-escalating cohorts of 4 patients, 4 patients, or 8-12 patients in order to obtain a total of 16 to 20 patients completing the study. Each cohort will receive one of three doses of omigapil daily for 12 weeks. In the event of a patient drop out, study investigators will replace the patient with another from the same stratum. Patients who discontinue study drug or express intent to withdraw will be asked to return for a final safety follow-up visit prior to withdrawal. Furthermore, patients who are withdrawn due to safety reasons (e.g. AE, SAE) will be followed up with safety calls and may be requested to return for study visits for safety assessments to be performed as necessary.

Statistical Methods Random assignment and dosing will be initiated in 16-20 patients to obtain a total minimum of 16 patients (4+4+8) who will complete the pharmacokinetic sample schedule.

This is a dose escalation study of omigapil in children and adolescent patients with CMD. It is planned that each participant will receive one of the 3 dose levels of omigapil (0.02 mg/kg, 0.08 mg/kg, or 0.2 mg/kg daily for 12 weeks). This dose range is expected to include a dose that achieves patient exposure within the target AUC_{0-24h} and C_{max} ranges. Dose determination will be based on the primary endpoint that a patient achieves a target AUC_{0-24h} range (3-33 ng.h/mL). Assuming dose-

proportional PK, based on data from 10 mg/kg by mouth (Novartis Study 0110073), the efficacious exposure range is expected to be in the range of 3-33 ng.h/mL (C_{max} 1.5-15 ng/ml) although based on animal modelling data, exposure at the upper end of this range is expected to be most efficacious (See Section 1.3 – Justification for dose for further details). The doses may be adjusted following the PK observed at the previous dose (see section 8.1). We aim to identify a dose under which the majority (90%) of patients will achieve the target AUC_{0-24h} range.

Four subjects will be treated at 0.02 mg/kg (level 1), and in case of no toxicity, dose escalation will occur after every 4 subjects until one or more patients exceed the target AUC_{0-24h} range. When this occurs, subsequent dose levels will be determined from the observed PK. Subsequent patients will be enrolled in groups of 4 using a CRM-type dose escalation/reduction design with the possibility to interpolate between pre-specified doses (Cheung, 2011). The proposed dose escalation algorithm adapts from a CRM-like algorithm called SAVOR that aims to identify a dose exceeding 33 ng.h/ml with 10% probability or less (Cheung, 2010). The upper end of the 3-33 ng.hr/ml will be targeted because some of the animal modelling (in CMD-relevant models) showed higher efficacy at 1 mg/kg compared to 0.1 mg/kg (Investigator Brochure, section 4.2.4). We will plan to enroll up to 20 patients, or when 8-12 subjects are enrolled to the dose shown to result in the target AUC_{0-24h} range (which may be less than the highest dose). Figure 1 (Section 10.10.3) shows the operating characteristics using simulation of SAVOR with 20 patients with group size of 4. Subjects who drop out will be replaced to meet a minimum requirement of 16 patients who complete the current study and will be chosen based upon their CMD subtype and weight in kg.

Patients will be stratified according to disease type and weight.

There will be no placebo group and assessment of safety and tolerability will include analysis of relevant data from the run-in periods for all cohorts.

Incidences of AEs/SAEs, severity and relationship of AEs/SAEs to study medication, and early withdrawal due to AEs/SAEs will be summarized using frequencies and percentages for each dose level of study medication and for the run-in periods. Incidences, laboratory abnormalities and physical examination results will be presented by visit for each dose level of study medication. ECG parameters will be summarized for each dose level using descriptive statistics.

- Pharmacokinetic parameters C_{max}, C_{min}, t_{max}, t_{1/2}, AUC_{0-t}, AUC_{0-8h}, AUC_{0-24h}*, λ_z, and R_o (*if sufficient data are available) will be

calculated and summarized by dose level of study medication using descriptive statistics.

Details of the planned analyses of the PK samples will be included in a separate Pharmacokinetic Analysis Plan.

Details of the planned analyses of the safety and efficacy data from the efficacy feasibility assessments will be outlined in a separate Statistical Analysis Plan.