Clinical Study Protocol

Study title: A phase Ib, open label study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending oral doses of Rimeporide in patients with Duchenne Muscular Dystrophy

Acronym: Rim4DMD

Sponsor: EspeRare Foundation
14 Chemin des Aulx
1228 Plan-les-Ouates
Switzerland

Study Sponsor’s number: ESPERARE_RIM_001

EudraCT number: 2015-002530-50

Version: 2.1

Date: February 19th, 2016

Amendment number: 2

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Investigator Agreement

Protocol Number: EspeRare_RIM_001
EudraCT Number: 2015-002530-50
Protocol version and date: 2.1. February 19th 2016
Sponsor: EspeRare Foundation

Study drug: Rimeporide.
Study title: A phase Ib, open label study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending oral doses of rimeporide in patients with Duchenne Muscular Dystrophy.
Acronym: Rim4DMD.

Investigator endorsement:

I, the undersigned, am responsible for the conduct of this study at this site and agree to conduct the study according to the protocol and any approved protocol amendments, study specific procedures, all applicable laws and regulatory authority requirements including but not limited to European directives, ICH Good Clinical Practice (GCP), the Ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.
Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.
I have read and understand fully the Investigator Brochure for rimeporide and I am familiar with the investigational product and its use according to this protocol.

_____________________________________________  ____________________________
Site Investigator’ Signature                       Date of signature
(DD MM YYYY)

_____________________________________________
Site Investigator’s Name and title (print)

CONTACT LIST

EudraCT Number 2015-002530-50


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Study Location: Multicentre study

Study Investigator coordinator: Professor Francesco Muntoni, FRCPCH, FMedSci

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SIGNATURE PAGE

**Protocol Number:** EspeRare_RIM_001  
**EudraCT Number:** 2015-002530-50  
**Protocol version and date:** 2.1 February 19th 2016  
**Sponsor:** EspeRare Foundation

**Study drug:** Rimeporide

**Study title:** A phase Ib, open label study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending oral doses of rimeporide in patients with Duchenne Muscular Dystrophy.

**Acronym:** Rim4DMD.

**This protocol has been approved by:**

**Name:** Professor Francesco Muntoni

**Trial Role:** Study Investigator coordinator.

**Signature:**

**Date**

This protocol describes the Rim4DMD clinical trial and provides information about procedures for patients taking part in the Rim4DMD trial. The protocol should not be used as a guide for treatment of patients not taking part in the Rim4DMD trial.
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**Acronym:** Rim4DMD.

**This protocol has been approved by:**

**Name:** Florence Porte Thomé

**Trial Role:** Research and Development Director at EspeRare Foundation

**Signature:**

**Date**

This protocol describes the Rim4DMD clinical trial and provides information about procedures for patients taking part in the Rim4DMD trial. The protocol should not be used as a guide for treatment of patients not taking part in the Rim4DMD trial.
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Acronym: Rim4DMD.

This protocol has been approved by:

Name: Dr Julian Gray
Trial Role: Medical advisor

Signature:

Date

This protocol describes the Rim4DMD clinical trial and provides information about procedures for patients taking part in the Rim4DMD trial. The protocol should not be used as a guide for treatment of patients not taking part in the Rim4DMD trial.
AMENDMENT(S)

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version:

<table>
<thead>
<tr>
<th>Protocol version number</th>
<th>Date of amendment</th>
<th>Type of amendment</th>
</tr>
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<tbody>
<tr>
<td>2.0</td>
<td>December 15th 2015</td>
<td>Substantial</td>
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</table>

Summary of main amendments:

Page 34 section 4.1.1 inclusion criteria: I.5: Ability to swallow capsules has been added

Page 35 section 4.1.2 Exclusion criteria E.10. has been added. E17 has been extended to all patients

Page 30 2.1.2 Secondary objectives and 2.1.3 Exploratory objectives
The biomarkers endpoints in the study are reclassified as exploratory.

Page 31 sections 2.2.1 Primary endpoints and 2.2.2 Secondary endpoints and 2.2.3 Exploratory
• For safety parameters: to correct the inconsistencies with the content of the protocol. Serum gastrin level will be measured only at the beginning and end of the study and will not be used for routine safety assessment during the study.
• To correct the classification of secondary endpoints according to the changes performed in the study secondary and exploratory objectives

Page 33 (new section called recruitment plan)
• For safety reasons, the SMC has advised that a time interval of at least one week should be maintained between administrations of the first dose in the first three patients in each cohort.
• It has been clarified also that recruitment is competitive.
• The duration of the recruitment period has been corrected: 12 months instead of 15 months which is the duration of the overall study as initially indicated in the Study Duration section.

Pages 33 to 34 sections 3.1 to 3.5 screening period, Treatment period and Follow-up.
• It is clarified in the text that 5 patients per cohort will be enrolled.
• It is proposed that the patient will be followed for 1-2 weeks rather than 2 weeks after either the planned end of treatment at week 4 or after premature discontinuation of treatment. This is because any withdrawal phenomena are expected to be apparent within one week in view of the short half-life of the compound.
• An additional safety visit after one week of treatment is added to further enhance safety monitoring.
• The visits followed by the patients during the study have been written in more detail to increase clarity.
• The process of reviewing data concerning eligibility of subjects at screening by the medical advisor is detailed in the protocol.

Page 36 section 5.1.4.2 Administration
• The relationship between timing of intake of study medication and food is clarified.
• The procedure to follow if patients have difficulty swallowing the capsules at the first administration is detailed in the protocol.
• The timing between intake of the study medication and other medications is detailed in the protocol.
• The table 2: Number of rimeporide capsules of 25mg or 50mg to be administered per dose and per day has been updated given the flexibility window for each study visits at hospital (+/-2 day) and dispensing frequency.

Page 38 section 5.1.4.2 drug dispensing
The local pharmacy may, if required for logistical reasons, deliver to the investigator to provide to the patient the study treatment medication needed to cover 1 week (+/-2 days) of treatment period the day before the Study Day 1 (SD1) if the patient eligibility is confirmed. For this purpose, before any prescription, the eligibility criteria including any AE, physical abnormalities, and changes in concomitant medications must be re-verified on day 1 by the investigator before prescribing the study drug.
Page 38 Section 5.3.1 Possible concomitant therapies

Page 39 Section 5.3.2 Prohibited therapies

- To avoid potential drug-drug interactions at the renal level, prohibited concomitant medications have been amended to exclude concomitant use of antibiotics with predominant renal secretion (e.g., cephalosporins), immunosuppressive agents with the exception of corticosteroids, continuous treatment with non-steroidal, anti-inflammatory drugs (NSAIDs), or lithium to reflect the guidance regarding exclusion of renally eliminated agents as listed in the IB.
- It is clarified that the use of prescription or over the counter medications should be approved by the investigator except in an emergency.

Page 40 Section 5.5 Photosensitivity guidance

The UV spectrum of Rimeporide shows the longest wavelength absorption band at 282.5 nm. No absorbance is observed at higher wavelength. Consequently, and in accordance with the ICH guideline S10, since Rimeporide does not absorb light within the range of natural sunlight (290nm-700nm), treatment with Rimeporide is considered not to pose a risk of photosensitivity and therefore no special guidance for patients on this issue is required.

Page 42 Section 6.3 Supine and standing blood pressure

In order to have a full picture of any potential effects of the study medication on blood pressure, blood pressure will be measured in both supine and standing positions at all visits.

Page 42 Section 6.5 Monitoring of ECG evolution parameters (including QTc)

ECG must be read by a local cardiologist as ongoing basis. The following parameters must be recorded: Heart Rate, PR Interval, QRS Duration, QT Interval, QTcB Interval, QTcF, and QRS Axis.

ECGs will be read centrally at the end of the study.

Pages 43 to 49 Sections 6.9 to 6.11 Safety blood and urine analysis and Pharmacodynamics and pharmacokinetics endpoints

- In order to be in accordance with the WHO guidance concerning the maximum blood volume to be collected in children within 24 hours, we will collect the blood samples for all the exploratory PD biomarkers at screening (once patients and parents have sign the consent) instead of at the study day 1.
- Local and central blood tests have been updated: troponin I has been removed. Others biomarkers to monitor muscle damage will be measured within central laboratories.
- Gastrin levels will be measured only at day 1 and day 28 as this is not required for routine safety monitoring.
- CRP levels will be measured only at Screening and day 28 as this is not required for routine safety monitoring.
- The method use for population PK analysis has been changed and will be described in a separate PK analysis plan.
- The volume of blood drawn over the whole study per subject has been increased to 60 ml from 48 ml. The fact that this volume refers to the total amount over the study (8 to 10 weeks) rather than the volume at each visit has been corrected.

Page 50 Section 7.1 screening

The procedure for review of eligibility data by the sponsor’s medical advisor is re-stated in this section. The necessity to obtain informed consent/assent prior to conducting any study procedures is added.

Page 51 Section 7.3.1.1 Confirmation of patient eligibility at study day 1 (SD1)

The need to confirm patient eligibility on the day of dosing is stated. Procedures regarding handling of screening failures is detailed.

Page 51 and 55 NMRI (NMRS if applicable) before first dose at day 1 and day 27

Due to technical difficulties in measurement of 31 phosphor NMRS and 23 sodium MRI, this measurement will be limited to patient enrolled in France who will undergo this procedure at the study site in Paris. Such patients will also undergo standard NMRI imaging in Paris. Patients in other countries will undergo only standard NMRI which will be performed locally.
**Page 53 section 7.3.5 After the Second dose of rimeporide**
Patients will be kept under observation for at least 6 hours after the second dose of study medication. Temperature (tympanic), heart and respiratory rate, blood pressure (supine and standing) will be repeated at 1 hour, 2 hours and 4 and 6 hours after the second administration of study medication.

**Page 54 section 7.5 week 1 (day 7+/− 2days)**
An additional safety visit after one week of treatment is added to further enhance safety monitoring.

**Page 56 section 7.11 Withdrawal Visit (1-2 weeks +/- 2 days after decision)**
As requested by the SMC, patients will be requested to continue to be followed up according to the study protocol even if they have discontinued the study medication. Corresponding text has been added to the study protocol. Patients discontinuing the study will be asked to confirm that their data and biological samples can continue to be used.

**Pages 62 section 8.2.1 Suspected Unexpected Serious Adverse Reactions Reporting**
The text regarding definition of serious adverse reactions and SUSARs has been corrected as per the request of the UK regulatory authority (MHRA).

**Page 65 section 9.1 to 9.2 stopping rules**
- The corresponding grading of adverse events in terms of severity has been specified according to the request of the MHRA i.e. Grade I= mild, Grade II = Moderate, Grade III = severe).
- Handling of cases of suspension of dosing at the individual level will be conducted primarily by the medical advisor with the investigator, with consultation of the SMC as needed, rather than primarily by the SMC to ensure a sufficiently rapid response.
- The stopping rule regarding elevation of serum creatinine is altered to use Cystatin C instead of creatinine since the latter is usually abnormally low in patients with DMD.

| Synopsis and section 2.2.3 Exploratory endpoints on pages 14 and 31; section 6.10 PD endpoints on page 46; blood samples volumes on page 48, section 7.1 screening page 48, section 7.5 week 2 on page 53, section 7.8 week 4 on page 54: The exploratory biomarkers: Plasma/ Serum levels of myomesin-3, miRNAs panel and the fibrosis biomarkers MMP-9 and the urine samples to follow the concentration of titin fragments have been removed. The nature of the other exploratory biomarkers that have been added in the version 2.0 has been clarified: these Blood samples will be collected for further investigation and namely to evaluate other cytokines involved in the inflammatory processes and to target several RNA coding for key proteins in DMD. | February 19th 2016 | Non substantial |

**Page 16 and 52 schedule of assessment and section 7.3.1.1 Confirmation of patient eligibility at Study day 1:** The term randomisation has been added by error. The PK sampling profile will be allocated as described initially in the section 6.10.2 “The sampling time points will be allocated to patients according to their inclusion order into the study” and as initially approved in the initial protocol version.

**Pages 42 sections 6.3 supine and standing blood pressure; page 43 section 6.4 heart rate and respiration rate; section 7 outline of study procedures.** In the substantial amendment of the protocol version 2.0, it has been approved that In order to have a full picture of any potential effects of the study medication on blood pressure, blood pressure will be measured in both supine and standing positions at all visits. Several inconsistencies throughout the protocol concerning the positions in which the blood pressure is measured have been identified and corrected in the herein version 2.1. It has been also clarified the corresponding positions for the heart rate measurement.

**Page 37 section 5.1.4.2 Administration**
The format of the table 2: Number of rimeporide capsules of 25mg or 50mg to be administered per dose and per day has been modified for clarification.

**Page 50_ Confirmation of patient eligibility at study day 1 (SD1)**
The process to be followed for the screening data review by the medical advisor has been updated.
# STUDY SYNOPSIS

**Title:** A phase Ib, open label study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending oral doses of rimeporide in patients with Duchenne Muscular Dystrophy (DMD)

**Study Acronym:** RIM4DMD

**Sponsor:** EspeRare Fondation, Switzerland

**Version and Date:** 2.1_ February 19th, 2016

**Sponsor protocol Number:** EspeRare_RIM_001

**EudraCT Number:** 2015-002530-50

**Coordinating Investigator:** Professor Francesco Muntoni, FRCPCH, FMedSci

UCL Institute of Child Health and Great Ormond Street Hospital, UK.

**Number of Sites:** 4 specialized sites in EU will participate in this study.

- UCL Institute of Child Health and Great Ormond Street Hospital, London, United Kingdom.
- Armand Trousseau Hospital, I-Motion unit, Paris, France
- San Raffaele Hospital, Milan, Italy.
- Santa Creu i Sant Pau Hospital, Barcelona, Spain.

**Indication:** Duchenne Muscular Dystrophy (DMD).

**Study Type, Phase and Design:**

- Interventional Phase Ib study.
- Open-label, multiple ascending oral doses, international multicentre pilot study.

**Study Population:**

- Ambulant DMD paediatric patients.

- Duchenne muscular dystrophy genetically confirmed;
- Males between 6 and 14 years old;
- Able to walk independently at least 75 meters;
- Patients on a stable dose of corticosteroids at least 6 months prior to baseline;

**Inclusion Criteria:**

- Patients able to swallow capsules size 4 according to the parents and investigator opinion;
- Willing and able to comply with all protocol requirements and procedures;
- Signed informed consents by the parent(s)/legal guardian(s);
- France only: Affiliated to or a beneficiary of a social security system.
Exclusion Criteria:

- Patients with significant renal disease or impairment, with Glomerular Filtration Rate estimated using plasma cystatin C level using the Filler formula less than 90ml/min/1.73m²
- Current or history of liver disease or impairment,
- History of any significant medical disorder which may confound the interpretation of either efficacy or safety data e.g. inflammatory, coagulation disease, unstable cardiac or respiratory disease
- Acute illness within 4 weeks of the first administration of study medication which may interfere with study assessments;
- Significant change of dosage and/or dosing regimens for corticosteroids planned for the duration of study medication;
- Use of beta blockers / and ACEI or ARB unless at stable dose for at least 3 months prior to baseline;
- Use of Proton Pump Inhibitors unless at a stable dose for at least 3 months prior to baseline
- Use of aldosterone antagonists (i.e. spironolactone, eplerenone) within 3 months prior to first administration of study medication;
- Use of anticoagulants, antithrombotics or antiplatelet agents,
- Use of antibiotics with predominant renal secretion (e.g., cephalosporins), immunosuppressive agents exception corticosteroids, continuous treatment with non-steroidal, anti-inflammatory drugs (NSAIDs), or lithium;
- Previous treatment with idebenone or other forms of Coenzyme Q10 within 1 month of the first administration of study medication;
- Previous treatment with investigational drugs within 4 weeks (or 7 half-life if longer than 4 weeks) of the first administration of study medication including placebo;
- A baseline QTc>450msec,or history of risk factors for torsades de pointes (eg, heart failure, hypokalaemia, family history of long QT syndrome);
- LVEF ≤ 45% at screening or within the past 6 months and/or history of acute heart failure;
- Ventilator dependent;
- Known individual hypersensitivity to any of the ingredients/excipients of the study medication;
- Patients with specific contraindication to MRI (e.g.: metallic foreign body, claustrophobia, etc.).
### Study Drug:
- Rimeporide (EMD 87580): 25-mg and 50-mg hard gel capsules.

### Dosing Regimen

#### Frequency of Administration:
- Multiple oral doses of rimeporide ranging from 50 to 300 mg administered three times a day will be evaluated in patients with Duchenne Muscular Dystrophy.
- The following doses will be studied sequentially in ascending order: 50 mg, 100 mg, 150 and 200 mg TID in patients with a body weight less than or equal to 30 kg at baseline; and 75 mg, 150, 200 and 300 mg TID in patients with a body weight more than 30 kg at baseline. Safety will be reviewed by the Safety Monitoring Committee before each dose escalation is undertaken.

### Treatment Duration:
- Rimeporide administration is foreseen for 4 weeks, with a two week follow-up period.

### Background Therapy

#### Concomitant Medication:
- Rimeporide will be administered on a background of corticosteroids with or without the addition of stable ACEI/ARB medication.

### Study objectives

#### Primary objective:
- To determine the preliminary safety and tolerability profile of multiple oral administrations of rimeporide.

#### Secondary objectives:
- **Pharmacokinetics:** To evaluate the pharmacokinetic profile of rimeporide in pediatric patients with DMD.

#### Exploratory objectives:
- **Pharmacodynamics/ pharmacokinetics:**
  - To measure inflammatory and muscular injury biomarkers;
  - To explore the PK/PD relationship of a 4-week rimeporide treatment on those surrogate biomarkers.
  - To explore the relationship between safety endpoints and pharmacokinetic parameters
- For all patients: To explore using Nuclear Magnetic Resonance (NMR) imaging the effect of a 4-week treatment with rimeporide on biomarkers including degree of inflammation, oedema, fat fraction, muscle composition.
• For patients recruited in Paris: To explore using Nuclear Magnetic Resonance (NMR) Spectroscopy the effect of a 4-week treatment with rimeporide on biomarkers including intracellular pH and intracellular Na.

**Study endpoints**

**Primary endpoints:**
- **Safety parameters**
  - Incidence, severity, causality and outcomes of AEs and SAEs
  - Vital signs, Supine and standing blood pressure, heart rate and respiratory rate
  - Substantial changes in laboratory parameters from blood and urine samples.
  - Number of patients withdrawn for safety issues

**Secondary endpoints:**
- **Pharmacokinetic profile of rimeporide in plasma** derived from modelling using sparse sampling: blood samples will be collected at different time points to determine the pharmacokinetic profile of orally administered rimeporide in plasma.

**Exploratory endpoints:**

**Pharmacodynamics**
- **Changes of plasma/ serum biomarkers:**
  - Plasma/ Serum levels of the inflammation markers: C - reactive protein (CRP), Tumor Necrosis Factor alfa (TNFα), Transforming Growth Factor beta (TGFβ-1) and other exploratory biomarkers to monitor muscle damages (cytokine panels and specific RNA targeting);

- **For all patients:** Changes in NMRI indices in skeletal muscle will be explored through NMRI indices (water T2, fat fraction).
- **For patients recruited in France:** Changes in NMRS indices in skeletal muscle will be explored through:
  - 31P NMRS indices;
  - 23Na NMRS indices may also be included.
<table>
<thead>
<tr>
<th>Study Safety Monitoring:</th>
<th>• A Safety Monitoring Committee (SMC) will oversee the study conduct, reviewing safety data generated at the end of each cohort. Safety assessment will be done on data collected in each cohort and during the 4 weeks treatment and 1-2 weeks of follow-up. The decision to progress to the next higher dose will be made after safety and tolerability data are reviewed for the preceding dose for 5 patients by a data Safety Monitoring Committee and determined that it is safe to proceed to the next dose level.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statistical Analysis:</td>
<td>• Descriptive statistics will be used to analyse the data. In view of the small sample size no formal hypothesis testing will be undertaken.</td>
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<tr>
<td>Sample Size:</td>
<td>• 20 completed patients with 4 cohorts of 5 patients each will participate in this pilot study.</td>
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<tr>
<td>Recruitment Duration:</td>
<td>• The recruitment period will vary depending on the recruitment speed; the objective being to recruit the foreseen 20 evaluable patients within 12 months.</td>
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<td></td>
<td>• Recruitment will be competitive among the 4 participating sites.</td>
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<td></td>
<td>• For each cohort, the first 3 patients must receive rimeporide with an interval of at least 1 week. If no safety issue is raised for the first 3 patients, then patients 4 and 5 can receive their first study treatment administration without a minimum time interval.</td>
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<tr>
<td>Study Duration:</td>
<td>• Expected study duration: 15 months</td>
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<tr>
<td>Study End Definition:</td>
<td>• End of the study is defined as last patient last visit.</td>
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### Table 1: Schedule of Assessments

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<th>V5</th>
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<th>V4</th>
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<td>X&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>X&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
<td></td>
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<td>X</td>
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</table>

(a) The day before the SD1  
(b) Day 27 +/- 2 days, just before the end of treatment period.  
(c) See section 5.1.4.2 drug dispensing of this protocol.
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<th>Term</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>aPTT</td>
<td>Activated Prothrombin Time</td>
</tr>
<tr>
<td>ARB</td>
<td>Angiotensin receptor blockers</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>ATG</td>
<td>Anti-thymocyte globulin</td>
</tr>
<tr>
<td>AUC</td>
<td>Area Under the Curve</td>
</tr>
<tr>
<td>BSA</td>
<td>Body Surface Area</td>
</tr>
<tr>
<td>CBC</td>
<td>Complete blood cell count</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CL</td>
<td>Systemic drug clearance</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>Peak drug plasma concentration</td>
</tr>
<tr>
<td>CMH</td>
<td>Cardiomyopathic hamster</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>C&lt;sub&gt;trough&lt;/sub&gt;</td>
<td>Plasma drug concentration immediately prior next dosing</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronic case report form</td>
</tr>
<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
</tr>
<tr>
<td>EOS</td>
<td>End of Study</td>
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<tr>
<td>GRMD</td>
<td>Golden retriever muscular dystrophy</td>
</tr>
<tr>
<td>ICMJE</td>
<td>International Committee of Medical Journal Editors</td>
</tr>
<tr>
<td>IMP</td>
<td>Investigational medicinal product</td>
</tr>
<tr>
<td>IFNγ</td>
<td>Interferon gamma</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>KD</td>
<td>Dissociation constant</td>
</tr>
<tr>
<td>KO</td>
<td>Knock Out</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
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</tr>
<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Matrix metalloproteinase</td>
</tr>
<tr>
<td>NCX</td>
<td>Sodium-calcium exchanger</td>
</tr>
<tr>
<td>NMRI</td>
<td>Nuclear Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NMRS</td>
<td>Nuclear Magnetic Resonance Spectroscopy</td>
</tr>
<tr>
<td>NaCl</td>
<td>Sodium Chloride</td>
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<td>ODD</td>
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<td>OPN</td>
<td>Osteopontin</td>
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<tr>
<td>PCR</td>
<td>Polymerase chain reaction</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>PPD</td>
<td>Purified protein derivative</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton-pump inhibitor</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SAD</td>
<td>Single ascending dose</td>
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<tr>
<td>SMC</td>
<td>Safety Monitoring Committee</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Reaction</td>
</tr>
<tr>
<td>t1/2</td>
<td>Elimination half-life</td>
</tr>
<tr>
<td>TGFβ</td>
<td>Transforming growth factor beta</td>
</tr>
<tr>
<td>Tmax</td>
<td>Time when plasma concentration is at peak</td>
</tr>
<tr>
<td>TMDD</td>
<td>Target mediated drug disposition</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial Master File</td>
</tr>
<tr>
<td>TNFα</td>
<td>Tumor necrosis factor alfa</td>
</tr>
<tr>
<td>WD</td>
<td>Withdrawal</td>
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PART I

1 BACKGROUND INFORMATION

1.1 DUCHENNE MUSCULAR DYSTROPHY (DMD)

1.1.1 Description of the Disease

Duchenne muscular dystrophy is a genetic disorder characterized by the progressive loss and degeneration of skeletal muscle, primarily in boys. DMD affects approximately 1 in 3,802 to 6,291 live male births worldwide (Mendell, 2012) (Moat SJ, 2013). The condition is inherited in an X-linked manner. Mutations in the DMD gene lead to the disease by preventing the expression of a key protein called dystrophin, an important structural component in muscle tissue. The lack of the protein dystrophin leads to membrane instability and uncontrolled calcium influx which contributes to the degenerative process (Iwata Y and Wakabyashi 2012).

Muscle weakness generally becomes apparent in the first few years of life with a delay in motor milestones, and a mean age of walking around 18 months. Children with DMD typically display skeletal muscle weakness by the age of 2–6 years and are diagnosed around the age of 5 years when typical motor function delays are apparent. Progressive muscle weakness leads to a loss of independent ambulation before the age of thirteen without disease modifying treatment. In non-ambulatory boys and young men, there is gradual loss of upper limb and neck functions, so that grooming, toileting, bathing, dressing, and eating become impaired or impossible to do independently, affecting the quality of life of patient, their caregivers and families.

Weakness in the limbs is accompanied by involvement of the respiratory muscles. By the age of 15 to 18 years, most patients with DMD start to develop serious respiratory complications, leading to the need for ventilatory assistance at night. Involvement of the heart muscles (cardiomyopathy) is also a universal phenomenon. Structural and functional changes associated with cardiomyopathy precede clinical manifestations. Cardiomyopathy is characterised by normal or thinned left ventricular (LV) wall thickness and progressive decline in ejection fraction or fractional shortening and clinical symptoms of congestive heart failure including (pulmonary) oedema, fatigue, dizziness and arrhythmia. Immobility of patients can temporarily disguise clinical manifestation of cardiomyopathy. However, in the late stage of the disease cardiomyopathy is severe and symptomatic and a major cause of death.

While advances in respiratory care have improved respiratory outcomes, dilated cardiomyopathy and heart failure remain the leading causes of death in patients with DMD. Patients rarely survive beyond early adulthood and the current average life expectancy is 27 years (DMD Patient Leaflet, 2013).
Natural history studies have shown that the use of corticosteroids and the management of spine deformity, pulmonary and cardiac dysfunctions have altered the timing of some of the clinical milestones of the disease. But with limited medical management have come new complications, and, quality of life often suffers. Once ambulation or some other functional capacity is lost in an individual with Duchenne Muscular Dystrophy, it is gone forever and sudden death may occur at any time, even in younger boys.

1.1.2 Currently available therapies
There is currently no known cure for patients with Duchenne muscular dystrophy. Recently, in the EU, the orphan drug, Ataluren (Translarna), has received conditional approval for treatment of DMD resulting from stop codon mutations in ambulatory patients aged 5 years and older. Approximately 13% of patients with DMD have stop codon mutations and are, thus, eligible for treatment with Ataluren, thus this treatment has potential benefit in a small proportion of DMD patients. Ataluren has not been shown to prevent cardiomyopathy. Corticosteroids, such as prednisolone and deflazacort, are the only drugs currently available which can help improve muscle function in DMD (MedlinePlus, 2014). However, although they may slow the progression of the disease, they have only been shown to be effective for six months to two years (NHS choices, 2013) and are not licensed for use in this condition. Their side-effects, especially with long-term treatment, can lead to complications. These include weight gain, which can further compromise mobility and a reduction in bone mineral density with increased risk of fractures, diabetes, cataracts and raised intraocular pressure can also occur (Angelini C., 2012). Steroid therapy (dose, frequency and duration of administration) is handled with notable differences across centres. However, it is rarely continued beyond the mid teen age years because of the side effects.

There are other unlicensed treatments and supplements which are also used to help alleviate signs and symptoms, such as albuterol and coenzyme Q10, although their efficacy is unknown. Additional treatments aimed at relieving particular aspects of the disease, which often worsen as it progresses, are also often required. These include orthopaedic appliances, treatment for heart failure, such as ACE-inhibitors, ARB, beta blockers and assisted ventilation to improve respiratory function. Non-pharmacological treatments can be very invasive, including corrective surgery for scoliosis and tendon contractures, insertion of a feeding tube when dysphagia prevents adequate nutrition and night-time ventilation when signs of respiratory failure become apparent.

In all patients, a mainstay of therapy is managing signs and symptoms of the condition and, therefore, needs to be tailored to the needs of an individual as their symptoms emerge and progress. The disease progresses despite treatment with steroids and/or ataluren in all patients, hence a significant unmet medical need exists that can only be addressed by additional treatments for DMD.
1.2 RIMEPORIDE

1.2.1 Description and mode of action

Rimeporide is a potent and selective inhibitor of the sodium-hydrogen exchanger (NHE-1). NHE-1 is a key membrane transporter regulating the intracellular pH, Na\(^+\) concentration, cell volume and catalyzing the electroneutral counter transport of Na\(^+\) and H\(^+\) through the plasma membrane (Orlowski et al., 2004). The NHE-1 isoform present on muscle fibers, is activated rapidly in response to various stimuli, causing a cascade of events leading to significant increase in intracellular [Na\(^+\)] and driving the Na\(^+\)/Ca\(^{2+}\) exchanger (NCX) into reverse mode hence, triggering an intracellular [Ca\(^{2+}\)] overload (Shi et al., 2013). NHE-1 inhibitors can block the activation of NHE-1, therefore decrease intracellular Na\(^+\) overload and, by normalizing the activity of the NCX, decrease intracellular Ca\(^{2+}\).

![Rimeporide mechanism of action](Figure 1)

Figure 1  Rimeporide mechanism of action (Modified from Stanbouly et al, 2008)

1.2.2 Preclinical Data

1.2.2.1 Non-clinical Pharmacology

The pharmacology of rimeporide has been investigated in a series of in vitro models and cellular assay systems. Rimeporide has subsequently been characterised as a highly selective and potent NHE-1 inhibitor. It has been demonstrated to have negligible activity on other cellular membrane transport systems, hormone receptors and ion channels and does not inhibit the binding of other ligands to these receptor systems. Rimeporide has been investigated in models of heart failure. In the post MI heart failure studies in rats (Pfeffer model) at London Ontario, the compound has been administrated for 3 months either immediately after MI, or 2 or 4 weeks after coronary ligation. In these studies, rimeporide markedly diminished the elevation of left ventricular end diastolic pressure and the loss of systolic function seen in non-treated controls with all treatment protocols. Left ventricular dilatation and hypertrophy as assessed by heart weight and by cell size as well as ANP expression were reversed to sham or near sham levels (Chen L, 2004).
Effects of rimeporide were also investigated in hereditary cardiomyopathic hamsters (CMHs). This sarcoglycan deficient model of cardiomyopathy and muscular dystrophy is indirectly related to Duchenne muscular dystrophy because sarcoglycans and dystrophin are part of a common dystrophin-glycoprotein complex (Blain et al 2011). Cardiomyopathy in CMHs is characterized by excessive intracellular Ca$^{2+}$ and Na$^+$ overload and increased NHE-1 expression. Treatment with rimeporide for 50 days prevented the increase of NHE-1 protein levels as well as Na$^+$ and Ca$^{2+}$ overload and necrosis. Treatment for 198 days prevented cardiac hypertrophy and necrosis (Chahine, et al., 2005). Treatment for 310 days prevented Na$^+$ and Ca$^{2+}$ overload, hypertrophy, and necrosis and reduced mortality of the hamsters from 73% in controls to 22% in treated animals (G. Bkaily, unpublished results. 

See IB rimeporide).

![Survival curve of CMHs after a 310-day treatment period. CM (n=26): untreated CMHs, Rimeporide (n=27): 310-days Rimeporide treated CMH. ***p<0.001 (See IB rimeporide).](image)

Curative treatment for 85 days with rimeporide which started in 275 days old CMHs was also effective to normalize NHE-1 expression, intracellular Na$^+$ and Ca$^{2+}$ levels as well as to reduce hypertrophy and prevent necrosis. Mortality during treatment was significantly reduced (Figure 2). The ACE inhibitor Cilazapril was not effective in this setting (Bkaily G 2015)

### 1.2.2.2 Toxicology

Repeated oral toxicity studies up to 26-week in rats and up to 39-week in beagle dogs were run. The main target organs were fundic parietal cells in rats and dogs; this finding is monitorable in the clinic by assessing gastrin levels as a surrogate marker for signs of adverse effects on the parietal cells.
No mutagenic activity and no teratogenic potential were shown. Rimeporide did not impair male and female fertility. The compound has no skin sensitizing properties and local tolerance studies revealed only minor effects after intra-arterial injection.

### 1.2.2.3 Safety pharmacology

No significant adverse effects were seen in specific studies of cardiovascular and renal function. The electrophysiological characterisation of rimeporide demonstrated that it has no pro-arrhythmic potential, even at very high concentrations.

### 1.2.3 Clinical Data

Seven Phase 1 clinical studies have been conducted with rimeporide. In these studies single oral, multiple oral and single iv doses of rimeporide have been investigated. To date, a total of 166 adult humans have received rimeporide comprising 145 healthy volunteers and 21 subjects with congestive heart failure (CHF), as the product was initially developed for this indication.

#### 1.2.3.1 Clinical pharmacokinetics

Following oral administration of rimeporide, Cmax values are reached in the range of 0.75 to 2.5 hours post dose in non-fasted and fasted adult healthy volunteers. Thereafter, concentrations decline rapidly, with a half-life of approximately 4 hours in healthy human volunteers. Pharmacokinetics of rimeporide is dose proportional in the range of 50 to 600 mg. No food effect was observed. Rimeporide is highly bioavailable by the oral route. Rimeporide is negligibly metabolized, with the major route for elimination of being clearance of unchanged drug via the renal route.

No pharmacokinetic drug-drug interaction (DDI) was found between digoxin and rimeporide and since rimeporide is not metabolized and neither induces nor inhibit CYP450 enzymes, no DDIs are expected with co-administered drugs which are metabolized by or affect the activity of these enzymes.

#### 1.2.3.2 Clinical experience to date

Rimeporide was well tolerated in healthy male subjects as single oral dose up to 600 mg, as multiple oral three times daily doses up to 3 x 200 mg for seven days, and as a single intravenous dose over 15 minutes up to 350 mg. A maximum tolerated dose could not be defined. Retrospective QT analysis of ECG data of the double-blind, placebo controlled oral single and multiple rising dose studies did not indicate an effect of rimeporide on prolongation of the QT interval. In studies with oral rimeporide, adverse events included chest discomfort, abdominal discomfort, postural dizziness, vaso-vagal episodes, dizziness, headache, lightheadedness, paresthesia, skin reactions (toxic erythema and urticaria), respiratory tract disorders, and diarrhea. After intravenous administration of rimeporide, elevated liver enzymes and a single case of an angioneurotic edema were reported. The relationship of the angioneurotic edema to study drug is considered remote. A total of five subjects were withdrawn
from phase I studies. Three subjects (one placebo, two on oral rimeporide) were withdrawn for a mild generalized skin reaction; two subjects were withdrawn for ECG abnormalities in the digoxin interaction study.

In a study with CHF patients, rimeporide given as a 50 mg or 100 mg dose up to three times daily for a total of eight days was well tolerated. The study drug had no adverse effects on blood pressure, heart rate, or on ECG parameters. Laboratory parameters including gastrin values appeared to be unaffected by the study drug. However, due to the small size of this clinical trial and the uncontrolled study design a definitive conclusion on the laboratory safety of rimeporide cannot be drawn from these trial data. One serious adverse event was reported (worsening heart failure), but considered unrelated to the study drug.

In conclusion, rimeporide was well tolerated in human healthy volunteers and in patients with CHF investigated so far.

1.3 **Rationale for Use of Rimeporide in DMD**

A pathological increase in intracellular free calcium has long been considered to be an important contributor to the pathophysiology of DMD (Cullighan et Ohlendieck 2002). Different factors are involved in causing this increase in calcium level.

First, lack of dystrophin leads to mechanical disruption of the sarcolemma, leading to leakage of calcium into the cells.

Secondly, enhanced calcium entry into the cells may occur secondary to a pathological increase in sodium (Na+) levels, which have been observed in skeletal and cardiac muscles of DMD patients (Weber et al 2012; Fanchaouy et al, 2009).

The increase in sodium level in the muscle cells in turn leads to enhancement of calcium entry through the so-called Na+/Ca2+ exchanger (NCX1) system (Burr, et al, 2014).

In 2007 Iwata et al (2007) published data showing that Cariporide, an NHE-1 inhibitor previously under development for treatment of cardiac failure, reduced intracellular sodium and calcium overloads in dystrophic muscle cells (mdx mice and BIO 14.6 hamster) and had significant beneficial effects on muscle functionalities and cellular mechanism in mdx mice (Iwata Y et al., 2007). NHE-1 inhibitors have also been shown to regulate a number of inflammatory processes (Yang et al., 2013) that are also involved in DMD pathophysiology (Evans et al., 2009).

Animal studies also provide support for the rationale of using rimepride, another NHE-1 inhibitor, in the treatment of DMD. In summary:

- Lifelong treatment with the rimeporide in the Syrian cardiomypathic hamster, a widely used model of cardiomyopathy, led to a marked decrease of intracellular sodium and calcium and a clear significant improvement in overall survival (Chahine et al., 2005).
In vitro studies have confirmed a potent effect of Rimeporide on NHE-1 expression and associated changes in intracellular pH in cultured wild type and dystrophic myotubes (Dorchies et al 2015)

In vivo studies in mdx mice showed reduced inflammation and fibrosis in skeletal muscle as well as in the diaphragm and heart muscles (Nagaraju et al 2014 and 2015).

On the basis of these preclinical findings, the European Medicines Agency recently granted Orphan Drug Designation to rimeporide for the treatment of Duchenne Muscular Dystrophy.

1.4 RATIONALE FOR DOSE SELECTION

Based on mdx mice and hamster efficacy studies, expected Rimeporide concentration required to achieve efficacy in patients with DMD is anticipated to be within the range of 500 – 2500ng/mL. Given the extensive pharmacokinetic data available from completed clinical studies in adult subjects, (including both healthy adult volunteers and patients with CHD) it has been possible to develop a pharmacokinetic model to determine the optimal dose regimen in paediatric patients with DMD. The proposed regimens of multiple ascending doses of 50mg, 100mg, 150mg and 200mg TID in patients with a body weight less than or equal to 30kg and of 75mg, 150mg, 200mg and 300mg TID in those patients with a body weight of greater than 30kg should enable a constant rimeporide plasma concentration within the estimated therapeutic range.

Doses of up to 200mg TID given daily for 10 days have been administered to adults in phase I studies and been found to be safe and well tolerated and doses up to 10 times the proposed maximum clinical dose have been evaluated in non-clinical studies thereby characterizing the anticipated safety profile.

Each dose level will be studied only after thorough evaluation of safety data in all subjects completing dosing at the previous dose level. Although the top dose of 200mg tid in patients with under 30kg body weight or 300 mg tid in patients with over 30kg body weight is higher than that studied in adult volunteers, this will only be administered if safety and tolerability are deemed acceptable by the safety monitoring committee at the previous dose level.
2 STUDY OBJECTIVES AND ENDPOINTS

2.1 STUDY OBJECTIVES

2.1.1 Primary objective:
- To determine the preliminary safety and tolerability profile of multiple oral administrations of rimeporide.

2.1.2 Secondary objective:
- Pharmacokinetics:
  - To obtain the pharmacokinetic profile of rimeporide in pediatric patients with DMD.

2.1.3 Exploratory objectives:
- Pharmacodynamics:
  - To measure inflammatory and muscular injury biomarkers;
  - To explore the PK/PD relationship of a 4-week rimeporide treatment on those surrogate biomarkers.
  - To explore the relationship between safety endpoints and pharmacokinetic parameters.
- For all patients: To measure noninvasively spectroscopy biomarkers after a 4-week treatment of rimeporide in patients with DMD NMR-I (inflammation, oedema, fat fraction, muscle composition). In particular:
  - To evaluate by NMR imaging:
    o Muscle water T2, proportion of muscle with elevated T2 which selectively measures muscle inflammation.
    o Heterogeneity of T2 within the muscle which reflects tissue disorganisation, fat fraction in the muscle.
- For patients recruited in Paris: To measure noninvasively spectroscopy biomarkers after a 4-week treatment of rimeporide in patients with DMD NMR-S (intracellular pH and intracellular Na). In particular:
  o To explore the PK/PD relationship of Rimeporide on intracellular pH, as measured by 31P Spectroscopy and on intracellular sodium, as measured by 23Na NMR spectroscopy;
2.2 STUDY ENDPOINTS

2.2.1 Primary endpoints:

- **Safety parameters** to be collected and assessed:
  - Incidence, severity, causality and outcomes of AE and SAE;
  - Vital signs, Supine and standing blood pressure, heart rate and respiratory rate;
  - Substantial changes in laboratory parameters from blood and urine samples;
  - Number of patients withdrawn for safety issues.

2.2.2 Secondary endpoints:

- **Pharmacokinetics parameters**: Pharmacokinetic profile of rimeporide in plasma derived from modelling using sparse sampling. Blood samples will be collected to determine the pharmacokinetic profile of orally administered rimeporide.

2.2.3 Exploratory endpoints:

- **Pharmacodynamics**: Exploratory evaluation of the early biological response of a 4 week treatment by rimeporide through changes of plasma / serum biomarkers:
  - Plasma / Serum levels of the inflammation markers: C - reactive protein (CRP), Tumor Necrosis Factor alfa (TNFα), Transforming Growth Factor beta (TGFβ-1) and other exploratory biomarkers to monitor muscle damages (cytokine panels and specific RNA targeting);

- **For all patients**: changes in NMRI indices in skeletal muscle will be explored through NMRI indices (water T2, fat fraction);

- **For patients recruited in Paris**: changes in NMRS indices in skeletal muscle will be explored through 31P NMRS indices and 23Na NMRS indices may also be included.

3 STUDY DESIGN
3.1 OVERALL DESIGN

This is a pilot phase Ib, open label, sequential-group study of ascending oral doses of rimeporide administered three-times daily (TID) for 28 days to patients with DMD.

The study foresees a screening, a treatment and a follow-up period.

There will be 4 dose levels. Patients with a body weight less than or equal to 30kg at baseline will be administered 50 or, 100, or 150 or 200-mg TID. Patients with a body weight more than 30kg at baseline will be administered 75 or 150 or 200 or 300-mg TID.

Each subject will participate in only 1 dose cohort and will receive rimeporide for a total of 4 weeks. 5 patients are expected to be recruited in each cohort through all participating sites.

Safety assessments will be made in the clinic at baseline, and after one, two and four weeks of treatment as well as 1-2 weeks following the end of treatment period or withdrawal of the study medication.

After the screening visit and if eligibility criteria are confirmed, patients will return to hospital for 4 study visits during the 4 week treatment period. The first 2 doses of study treatment will be taken in the clinic as well as the last dose 28 days later. In between, 2 safety visits at hospital are scheduled at weekly intervals during the 2 first weeks of study treatment. A phone call is also planned 3 weeks after the first dose to discuss the clinical condition of the patient, and note any possible adverse events reported by the patient or his parents.

Safety assessments will also be made in the clinic 1-2 weeks following the end of treatment period or after any premature withdrawal of the study medication. The details of examinations and tests that must be performed at study visits are provided in table 1 “Schedule of Assessments” and also in the subsequent sections of this protocol.

The decision to progress to the next higher dose will be made after safety and tolerability data are reviewed for the preceding dose for 5 patients by a data Safety Monitoring Committee and determined that it is safe to proceed to the next dose level.
3.2 RECRUITMENT PLAN

The recruitment of patients will be competitive over the 4 participating sites. For safety reason, Patients must be recruited in order to avoid first study treatment administration on the same day. For each cohort, the first 3 patients must receive rimeporide at an interval of at least 1 week. If no safety issue is raised for the first 3 patients, then patients 4 and 5 can receive their first study treatment administration without a minimum time interval.

3.3 SCREENING PERIOD

Screening will be carried out within 4 week prior to first administration of rimeporide (SD1) to enable confirmation of patient eligibility and following the signature of the Informed Consent Form. For each patient screened, an anonymized eligibility form must be sent by email to the Sponsor representative and medical advisor following the screening visit. This eligibility form summarizes the eligibility criteria, the concomitant medications, and the medical history. This form will be reviewed by the medical advisor to approve inclusion of each patient based on the screening data and to prevent protocol violations.

3.4 TREATMENT PERIOD

Rimeporide will be taken for 4 weeks, three times a day, after meals starting on Study Day 1 (SD1) and finishing on week 4 (28 days totally). After screening visit and if eligibility criteria are confirmed patients will return to hospital for 4 study visits during the 4 week treatment period. The first 2 doses of study treatment will be taken at hospital as well as the last dose 28 days later. In between, 2 safety
visits at hospital are scheduled each week during the 2 first weeks of study treatment. A phone call is also planned 3 week after the first dose to discuss the clinical conditions of the patient, and note any possible adverse event reported by the patient or his parents. The details of examinations and tests that must be performed at study visits are provided in table 1 “Schedule of Assessments” and also in the subsequent sections of this protocol.

### 3.5 FOLLOW-UP PERIOD AND END OF STUDY VISIT

All patients who have received at least one dose of rimeporide will be monitored for 1-2 weeks after the last administration of rimeporide, independently of the duration of treatment with rimeporide. A 1-2 weeks follow-up period is justified by rimeporide half-life (approximately 4h to 7h, with greater than 99% elimination of rimeporide being expected to occur within seven half-lives, i.e.: 28h to 49h). The details of examinations and tests that must be performed at the end of study visit are provided in table 1 “Schedule of Assessments” and also in the subsequent sections of this protocol.

### 4 TARGET POPULATION

#### 4.1 ELIGIBILITY CRITERIA

Patients included in the study must be compliant with the following inclusion/exclusion criteria:

##### 4.1.1 Inclusion Criteria

I.1. Duchenne muscular dystrophy genetically confirmed;
I.2. Males between 6 and 14 years old;
I.3. Able to walk independently at least 75 meters;
I.4. Patients on a stable dose of corticosteroids at least 6 months prior to baseline;
I.5. Patients able to swallow capsules size 4 according to the parents and investigator opinion;
I.6. Willing and able to comply with all protocol requirements and procedures;
I.7. Signed informed consents by the parent(s)/legal guardian(s);
I.8. France only: Affiliated to or a beneficiary of a social security system

##### 4.1.2 Exclusion Criteria

E.1. Patients with significant renal disease or impairment, with Glomerular Filtration Rate estimated using plasma cystatin C level using the Filler formula less than 90ml/min/1.73m²
E.2. Current or history of liver disease or impairment,
E.3. History of any significant medical disorder which may confound the interpretation of either efficacy or safety data e.g. inflammatory, coagulation disease, unstable cardiac or respiratory disease;
E.4. Acute illness within 4 weeks of the first administration of study medication which may interfere with study assessments;
E.5. Significant change of dosage and/or dosing regimens for corticosteroids planned for the duration of study medication;
E.6. Use of beta blockers / and ACEI or ARB unless at stable dose for at least 3 months prior to baseline;
E.7. Use of Proton Pump Inhibitors unless at a stable dose for at least 3 months prior to baseline
E.8. Use of aldosterone antagonists (i.e. spironolactone, eplerenone) within 3 months prior to first administration of study medication;
E.9. Use of anticoagulants, antithrombotics or antiplatelet agents,
E.10. Use of antibiotics with predominant renal secretion (e.g., cephalosporins), immunosuppressive agents exception corticosteroids, continuous treatment with non-steroidal, anti-inflammatory drugs (NSAIDs), or lithium;
E.11. Previous treatment with idebenone or other forms of Coenzyme Q10 within 1 month of the first administration of study medication;
E.12. Previous treatment with investigational drugs within 4 weeks (or 7 half-life if longer than 4 weeks) of the first administration of study medication including placebo;
E.13. A baseline QTc>450msec, or history of risk factors for torsades de pointes (eg, heart failure, hypokalaemia, family history of long QT syndrome);
E.14. LVEF≤ 45% at screening or within the past 6 months and/or history of acute heart failure;
E.15. Ventilator dependent;
E.16. Known individual hypersensitivity to any of the ingredients/excipients of the study medication;
E.17. Patients with specific contraindication to MRI (e.g.: metallic foreign body, claustrophobia, etc.).

5 DESCRIPTION OF IMP

Rimeporide (EMD 87 580), a benzoyl-guanidine derivative is a Na+/H+ exchange inhibitor for oral use. The full chemical name of EMD 87 580 is: N-(4,5-Bis methanesulfonyl-2-methyl-benzoyl)guanidine hydrochloride monohydrate
Rimeporide hard gelatine capsules at manufactured by GLATT and is supplied to study sites by PHAST. The nominal composition of the rimeporide is hard gelatin capsules. The capsules are immediate release formulations. The capsules contain mannitol, hydroxypropyl methylcellulose, low-substituted
hydroxypropyl cellulose, and magnesium stearate as excipients. These excipients are regarded as safe and conform to current pharmacopoeias.

5.1 IMP HANDLING

5.1.1 Packaging and Labelling
Rimeporide will be supplied to the sites in hard gel capsules in bottles of 50 capsules each. Doses will be supplied as 25mg or 50mg per capsules. The drug will be appropriately labeled in the local language and adapted to the national requirements.

5.1.2 IMP Supply
As the study is not blinded, rimeporide study medications will be supplied to the study sites as open-label supplies.

5.1.3 IMP Receipt and Storage
Rimeporide bottles will be transported with temperature deviation alarms, in order to ensure consistent temperatures during shipment. When the study drug is received at the site, the Pharmacist or designee will check for accurate delivery and absence of temperature deviation alarms. Storage is recommended at a room temperature not exceeding 25° C. All bottles must be stored in a secure locked location in a temperature-controlled room. Any deviations from the recommended storage conditions should be immediately reported to the Sponsor. Affected bottles should not be used and should be quarantined until the Sponsor has authorised their use. Pharmacist or its designee must check the conformity of the shipment with the QP release documentation sent with rimeporide bottles. Any discrepancies raised must be notified immediately to the sponsor. Bottles must be quarantined until Sponsor authorization.

5.1.4 IMP Preparation, Administration, Accountability and Destruction

5.1.4.1 Preparation
Investigation drug is provided as hard gel 25 mg or 50 mg capsules ready to be swallowed. No preparation is required.

5.1.4.2 Administration
Multiple oral doses of rimeporide ranging from 50 to 300 mg administered three times a day will be evaluated in patients with Duchenne as shown in the table below:
Each patient enrolled in the study will receive test drug under fed conditions three times a day. At each study visit, the patient will take his study treatment at hospital (the morning dose and lunch dose at SD1 but only the morning dose SD28). A standard meal will be taken within 30 minutes before drug administration for the purpose of evaluation PK profile during study visit 1 and 28 since food intake could impact the time at which the maximum serum concentration is achieved after that the drug has been administered ($t_{\text{max}}/C_{\text{max}}$) but has no influence on total drug exposure over time (AUC). The examinations and test timepoints proposed in this study are based on an expected $t_{\text{max}}$ of about 1.5 hours following a standard meal. There is no specific recommendation for food and fluid during the treatment period. Outside study visits at hospital patients can take their study treatment at their convenience after a meal. The drug product can be administered with any kind of fluid. Ideal time points are:
- Morning administration between 7:00 and 8:00 am (after breakfast);
- Afternoon administration between 12:00 and 1:00 pm (after lunch);
- Evening administration between 7:00 to 8:00 pm (after dinner).

However these time points could be adapted according to the local/patient habits.

<table>
<thead>
<tr>
<th>Cohorts</th>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight at baseline</td>
<td>≤ 30 kg</td>
<td>&gt; 30 kg</td>
<td>≤ 30 kg</td>
<td>&gt; 30 kg</td>
</tr>
<tr>
<td>Total dose (per Day)</td>
<td>150 mg</td>
<td>225 mg</td>
<td>300 mg</td>
<td>450 mg</td>
</tr>
<tr>
<td># 25 mg capsules</td>
<td>2 caps. TID (6 per days)</td>
<td>3 caps. TID (9 per days)</td>
<td>2 caps. TID (6 per day)</td>
<td>3 caps. TID (9 per day)</td>
</tr>
<tr>
<td># 50 mg capsules</td>
<td>5 bottles of 50 capsules (25 mg)</td>
<td>7 bottles of 50 capsules (25 mg)</td>
<td>5 bottles of 50 capsules (50 mg)</td>
<td>7 bottles of 50 capsules (50 mg)</td>
</tr>
</tbody>
</table>

Table 2: Number of rimeporide capsules of 25mg or 50mg to be administered per dose and per day
Capsules must be swallowed as a whole and not in combination with other medications. Capsules are sealed and could not be opened. At the first administration of the study treatment, if the patient does not succeed to swallow the capsules (e.g. vomiting, etc.), the dose must not be given again and patient must wait until the second dose administration. If the patient still cannot swallow the capsules, the patients will be withdrawn from the study.

5.1.4.3 Drug Dispensing

- At study day 1, each patient will receive all capsules needed for the first 7 days + 2 days overage of treatment.

The local pharmacy may, if required for logistical reasons, deliver to the investigator to provide to the patient the study treatment medication needed to cover 1 week (+/-2 days) of treatment period the day before the Study Day 1 (SD1) if the patient eligibility is confirmed.

For this purpose, before any prescription, a physical examination including vital signs and a 12 lead ECG must be performed by the investigator the day before the study Day 1 (SD1). A careful review of the AEs experienced by the patient and the potential concomitant medication changes occurred during the screening period must be reviewed by the investigator.

If the eligibility is confirmed, the Pharmacist is authorised to deliver the study medication to the investigator. Bottles will be kept then within the clinical unit in a secured place which meet the IMP storage conditions, the protocol and the ICH/GCP requirements until the morning of the day after (SD1).

At each subsequent study visit a new prescription will be made by the investigator and the local pharmacy will deliver the IMP needed to the investigator to provide to the patient as following:

- At Study day 7, each patient will receive all capsules needed for the next 7 days + 2 days overage of treatment;
- At study day 14, patients will receive all capsules needed for a further 16 days of treatment (14 days plus 2 days overage).

5.1.4.4 Accountability

When the study drug is received at the site, the Investigator or Pharmacist (or appropriate designee) should acknowledge its receipt by signing (or initialling) and dating the documentation. Documentation should be returned to Sponsor (or its designee) and a copy retained in the Investigator’s file. The dispensing of the study drug shall be carefully recorded on Drug Accountability Forms and an accurate accounting must be available for verification by the Monitor at each pharmacy monitoring visit.
Drug Accountability forms must be completed by pharmacist (or its designee) for each patient. Dispensing and return of unused drug (number of capsules) should be detailed on these forms. Drug accountability records shall include:

- Confirmation of the study drug’s delivery to the study site;
- The inventory at the study site;
- The use of study drug by each patient;
- The return to the Sponsor or alternative disposition of unused products.

The records should include dates, quantities, expiration dates, if applicable, and batch number and patient number. Unused study drug must not be discarded or used for any purpose other than the present study. Study drug that has been dispensed to a patient and returned unused must not be re-dispensed to a different patient.

### 5.1.4.5 Destruction, Return and Disposal

Pharmacy monitoring visit must be performed before any drug return request from site. Drug Accountability Forms will be verified before any arrangements for study drug return and authorisation of destruction. No destruction on site is planned. Any unused IMP should be returned to PHAST for destruction. A certificate of destruction will be send to site once performed.

### 5.2 PATIENT BACKGROUND TREATMENT AND CARE

#### 5.2.1 Background Therapy with corticosteroids

Rimeporide will be administered on a background of stable doses (for the last six months) of corticosteroids. Since medical management of DMD with corticosteroids tends to be individualized, there is not a recommended dose as background therapy in this study.

#### 5.2.2 Prophylactic treatment

No specific prophylaxis is required in DMD patients.

### 5.3 CONCOMITANT THERAPY

#### 5.3.1 Possible concomitant therapies

- Analgesic treatment, antibiotics, ACE inhibitors, ARB, beta-blockers and general supportive care (e.g. gastro-protective agents excluding Proton-Pump Inhibitors [PPIs] unless at stable dose for at least 3 months prior to baseline) are permitted within the study.
• Use of any additional prescription drugs or over-the-counter medication (including herbal and homeopathic preparations), with the exception of multi-vitamins, requires approval from the Investigator except in an emergency.

5.3.2 Prohibited therapies

• Use of aldosterone antagonists (i.e. spironolactone, eplerenone) within 3 months prior to first study medication administration and during treatment period.

• Use of anticoagulants, antithrombotics or antiplatelet agents, treatment with idebenone or other forms of Coenzyme Q10 within 1 month before the first administration of study medication and during treatment period.

• Previous treatment with other investigational drugs including placebo within 4 weeks (or seven half-lives) of the first administration of study medication and during treatment period. During treatment with rimeporide, no concomitant use of any other investigational drug is allowed.

• Proton Pump Inhibitors within 7 days of the first administration of study medication and during the treatment period unless at stable dose for at least 3 months prior to baseline to avoid confounding effects which might occur due to these agents on serum gastrin levels.

• Use of antibiotics with predominant renal secretion (e.g., cephalosporins), immunosuppressive agents exception corticosteroids, continuous treatment with non-steroidal, anti-inflammatory drugs (NSAIDs), or lithium.

5.4 CONTRACEPTION GUIDANCE

Contraception guidance: due to the age range of this patient population, their clinical conditions, the short study treatment period and the short half-life of the drug (4 hours), no specific guidance to avoid pregnancy of a partner is provided. Moreover in animal male fertility studies no evidence of impairment has been shown. However is important to remind to investigators that pregnancy must be avoided during any clinical study. This should be reminded also to patients and their parents if applicable.

5.5 PHOTOSENSITIVITY GUIDANCE

The UV spectrum of Rimeporide shows the longest wavelength absorption band at 282.5 nm. No absorbance is observed at higher wavelength. Consequently, and in accordance with the ICH guideline S10, since Rimeporide does not absorb light within the range of natural sunlight (290nm-700nm), treatment with Rimeporide is considered not to represent any photo safety risk or concern and therefore no special guidance for patients on this issue is required.
5.6 PATIENT STUDY CARD
In case of health problem, adverse events or symptoms, patients and parents will be asked to consult immediately the investigator to find out the most appropriate care that could be given to the patient. At Screening and before leaving the clinic, each patient (and/or patient’s legal representative) will be given a card to carry at all times in case of any visits to doctors or emergencies. The card gives details of the name of the drug, name of the responsible physician, and the address and telephone number of the study site. This card will be collected by the Investigator from the patient after the end of the study. Unless in case of emergency or the investigator has approved them beforehand, patients should not take new medicines during his study participation. This includes prescription drugs and over the counter medicine.

5.7 PATIENT DIARY
At screening, each patient will receive a diary to record:

- The time of each dose taken;
- The number of pills swallowed at each dose;
- The time of the end of the last meal or collation taken before each dose;
- Any missing dose;
- Any new symptom or illness, unusual complaint: the event must be described concisely. All medication taken to treat symptom must be recorded as well as the onset date, the end date and the duration of the events;
- Any changes performed on the medications (dosing, frequency, stop date, interruption, etc.)
- Any and all new medicine (including the over the counter medication or is a natural or herbal remedies and homeopathic preparation, etc.);
- Any unplanned hospital admission.

Precise instructions for diary completion should be given to patients and their parents or legal guardian at screening. Patients and parents will be asked to keep and bring any new prescription of concomitant medication to the investigator for review. The completed diary must be returned to the investigator and reviewed at each study visit at hospital.

5.8 RESCUE THERAPY
No specific rescue therapy is foreseen for DMD. Patients who are withdrawn from the study due to a safety issue will be treated according to the standard of care at the site.

6 STUDY ASSESSMENTS
Safety and tolerability of multiple doses of rimeporide will be assessed as follows:
6.1 ADVERSE EVENTS
An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.
A patient diary will be given to each patient at Screening. Any health problems, side effect, unusual complaint or symptoms including any unplanned hospital admissions must be described in this diary that should be returned to investigator at each study visit on site. Weekly after the first rimeporide administration a phone call will be made to discuss the clinical conditions of the patient, and note any possible adverse event reported by the patient or his parents.
On week 3, after the first rimeporide administration a phone call will be made to discuss the clinical conditions of the patient, and note any possible adverse event reported by the patient or his parents.
Any adverse event experienced by patients should be recorded in the eCRF. At each study visit on site, investigator will also review any experienced adverse event. Clinical significance, causality and severity of any experienced adverse event should be evaluated by the investigator according to patient health status.
Any enrolled subjects withdrawn for safety issue from the trial must be reported and explained on the eCRF.

6.2 PHYSICAL AND NEUROLOGICAL EXAMINATION
Weight will be recorded in kg and height in cm.
Physical examination will include assessment of the head, eyes, ears, nose, throat, heart, chest, lungs, abdomen, extremities, peripheral pulses, skin and any other physical conditions of note.
The neurological examination will include examination of the cranial nerves, upper and lower extremities for muscle strength, reflexes, sensation and cerebellar function.

6.3 SUPINE AND STANDING BLOOD PRESSURE
Blood pressure will be measured in the supine and standing positions at each study visit.
The supine blood pressure should be measured first and should be measured after the subject has been lying down for 5 minutes. The subject should then be asked to stand and the standing blood pressure should be measured after the subject has been standing for 2 minutes.
For each position, systolic and diastolic blood pressures will be measured with a standardized manometer; alternative validated methods of measurement may also be used. The point of disappearance of Korotkoff sounds (phase V) will be recorded as the diastolic blood pressure where a sphygmomanometer is used.
The same arm should not be used for blood collection and blood pressure assessments if possible. If there is a clinically important change in blood pressure from the previous reading, measurements will be repeated immediately to confirm the change.
6.4 HEART RATE AND RESPIRATORY RATE
Heart rate will be determined over 60 seconds following the recording of blood pressure in the corresponding position (supine and standing). Respiratory rate will be measured at rest by observation.

6.5 MONITORING OF ECG EVOLUTION PARAMETERS (INCLUDING QTC)
Heart function will be monitored by using a 12-lead ECG. ECG equipment should be recently serviced and calibrated. Machine calibration records and performance data should be maintained on file. ECG parameters will be obtained from replicate ECG measurements (the average of the parameters from 3 consecutive ECGs readings 5 minutes apart) to increase the precision of the potential changes in QTc. Care will be taken to perform ECG recording within one hour before first rimeporide dose intake and 1.5 hours after the first and the second dose. ECG must be read by a local cardiologist as ongoing basis. The following parameters must be recorded: Heart Rate, PR Interval, QRS Duration, QT Interval, QTcB Interval, QTcF, and QRS Axis.
ECGs will be read centrally at the end of the study.

6.6 SPIROMETRY: PULMONARY FUNCTION TESTS
The forced vital capacity (FVC), which is the volume delivered during an expiration made as forcefully and completely as possible starting from full inspiration, and the forced expiratory volume (FEV-1) in one second, which is the volume delivered in the first second of an FVC manoeuvre will be measured by a recently serviced and calibrated spirometer.

6.7 6-MINUTE WALK TEST
The 6-minute walk test (6MWT) has been the most commonly used primary outcome measure in clinical development programs at the time this guidance is being written. Current thinking is that in DMD, the 6-minute walk distance (6MWD) is a global / integrated measure of multiple systems involved in walking. In this study the 6MWT will be used only as screening test to evaluate the ability of the patient to walk (study is only exploratory at this stage and no efficacy is tested). Indeed ability to walk at least 75 m is an inclusion criteria. The test will be done according to a procedure detailed in a study specific manual.

6.8 ECHOCARDIOGRAPHY
Left ventricular ejection fraction will be evaluated by a cardiologist using standard echocardiographic techniques at the local centre at screening.
6.9 SAFETY HEMATOLOGY, BIOCHEMISTRY AND URINALYSIS

All safety laboratory tests should be recorded in the eCRF from the local laboratory. Normal values of local laboratory should be provided to the Sponsor before any patient’s inclusion on site and recorded into the eCRF. Clinical significance of any observed abnormality should be assessed by the investigator. Rules for AE reporting are described in adverse event section.

Blood and urinary samples for safety hematology, biochemistry and urinalysis will be **analysed on site** at each study visit as following:

**Haematology will include:**

- red blood cell count
- hemoglobin
- hematocrit
- red cell indices
- white blood cell count, including differential
- platelet count
- PT – visits 1 and 5 only
- aPTT - visits 1 and 5 only

**Biochemistry will include:**

- sodium, potassium, chloride, bicarbonate, calcium, inorganic phosphate
- urea
- creatinine
- cystatin C
- glucose
- total bilirubin
- total protein
- albumin
- aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase
- gamma GT
- creatine kinase (CK)
- cholesterol, triglycerides
- Uric acid.

**Only at Screening and SD28:** C-reactive protein

**Only at SD1 and SD28:** Gastrin (after 10 hours of fasting: no food or drink except for water)
Urine Analysis will include:

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<th>Microscopy</th>
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<td>pH</td>
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6.10 PHARMACOKINETIC ENDPOINTS

6.10.1 Optimal number of samples

The sampling schedule should be optimized for maximizing the chance to detect a difference between the population PK model predictions and the observations in the 20 patients to be enrolled. This optimality criterion is different from the usual D-optimality criterion, which maximizes the precision of parameter estimates. Hence, D-optimality is not relevant in this context. To the best of our knowledge, no optimality criterion has been proposed in our context. Therefore, we derive the sampling times by using a geometric sequence. This is reasonable, because the concentration versus time profile is described by a sum of exponential terms.

To evaluate the population PK model, we wish at day 1: one point in the absorption phase, one point near the $C_{\text{max}}$, and two points in the biphasic decay, i.e. four points at day 1. At week 4, we need only to verify the lack of time dependency of rimeporide PK. Two points are needed. Given that 20 patients will be enrolled, the amount of data for validation of the population PK model will be $20 \times 6 = 120$ points.

6.10.2 Sampling times

At day 1, for half of the patients, samples will be taken before first dose of rimeporide, and in the following time frames: (0.5 – 1h), (1 – 2h), (2.5 – 3.5h), 6h after the first dose.

For the other half of the patients, samples will be taken before first dose of rimeporide and in the following time frames: (0.5 – 1h), (1 – 2h), (2.5 – 3.5h), 6h after the second dose. In this way, samples will be taken up to 12h after the first dose, corresponding to approximately 3 half-lives.

The sampling time points will be allocated to patients according to their inclusion order into the study.

At week 4, samples will be taken in the following time frames: (0.5 – 1h), 6h after the last dose.

6.10.3 Blood samples collection, handling and storage

For the analysis of rimeporide, 1 to 1.5 ml blood samples should be taken by an indwelling catheter to avoid multiple needle punctures. Pain should be minimized by using indwelling catheters introduced under topical anaesthesia since repeated blood sampling is necessary. An anaesthetising patch should be proposed before the blood sample is taken to limit the pain associated with the introduction of the needle.
Each sample will be collected into a heparin-containing tube. Samples will be immediately be cooled at 0°C and centrifuged within 30 minutes at 4°C at 1500g for 10 minutes. Plasma will be separated into 2 equal aliquots of 200µl, rapidly transferred to a polypropylene tube, stoppered and stored at -20°C in a secured place until shipment to the central laboratory which carry out of the rimeporide plasma level determination. Each tube will be labelled with the following information: study acronym, protocol number, patient number, site number, study day, time point, date and time of the collection.

All plasma samples will be shipped by an authorized carrier after completion of each study cohort to the central laboratory in charge of the rimeporide plasma level determination according to the standard procedures provided by the sponsor in the laboratory manual. The samples will be transferred in a container filled with enough dry ice to ensure that the samples are kept frozen. Temperature will be controlled over the shipment. Plasma level of rimeporide will be valuated using a validated HPLC-MS/MS technique.

6.10.4 Pharmacokinetic analysis

Given that 20 patients will be enrolled, the amount of data for PK analysis will be 20 x 6= 120 points. These data will be analysed using a population approach also called non-linear mixed effects modelling. Due to the sparse sampling strategy, data originating from other clinical studies (e.g. Phase I studies in adult healthy volunteers), could be used in order to build a population pharmacokinetic model. All details regarding the PK analysis will be described in a separate document.

6.11 PHARMACODYNAMIC ENDPOINTS

6.10.1 Rationale

In DMD patients a persistent inflammatory response in their skeletal muscles leads to an altered extracellular environment, including an increased presence of inflammatory cells (e.g., macrophages) and elevated levels of various inflammatory cytokines and growth factors. Unfortunately, the signals that lead to successful muscle repair in healthy muscle may promote muscle wasting and fibrosis in dystrophic muscle30 (Gosselin 2004). Finally to evaluate the level of inflammation measurements of CRP, TNF-α and TGFβ will be made.

CRP is a positive acute phase protein produced by the liver in response to stimulation by interleukin (IL)-6, it represents a non-specific inflammatory biomarker of inflammation, widely measured in many different acute and chronic inflammation conditions. This protein will be monitored as exploratory marker even if with the available data the use of corticosteroids may already have normalized the value. TNF-α has been identified as another potentially useful marker as it is an early and potent pro-inflammatory cytokine that stimulates the inflammatory response; TNF-α increases rapidly within damaged myofibers and is expressed by myoblasts and myotubes. It was reported that the mean serum
TNF-α concentration in Duchenne muscular dystrophy patients was approximately 1,000 times higher than that in healthy subjects.31 (Abdel-Salam et al., 2011).

For assessment of a potential pharmacological effect in DMD, exploratory biomarkers, creatine kinase (CK) total, creatine kinase-MM fraction, mostly located in the skeletal muscle, and titin fragments have been selected to be monitored in the proposed clinical study. Those markers have been already used as markers for DMD of cardiac injury.

CK total and CK isoenzymes (that includes the MB fraction, mostly located in the myocardium, and the MM fraction, mostly located in the skeletal muscle) will be tested. CK-isoenzymes (namely CK-MM) is commonly used as a blood-based biomarker for muscular dystrophy to evaluate the level of muscle damage and necrosis. Measurement of CK concentration is performed routinely in hospital laboratories (Raman 2015).

Given that the intent of the proposed phase Ib study is exploratory for all the above listed biomarkers intra patients analysis will be performed when evaluating these potential markers. Blood samples will be also collected for further investigation and namely to evaluate other cytokines involved in the inflammatory processes and to target other RNA coding for key proteins in DMD.

6.11.1 Blood samples collection, handling and storage

For Creatine Kinase total and isoenzymes, Tumor necrosis factor alfa (TNFα), transforming growth factor beta (TGFβ-1) and other exploratory biomarkers to monitor muscle damages:

Creatine Kinase total and isoenzymes, Tumor necrosis factor alfa (TNFα), Transforming growth factor beta (TGFβ-1) measured from blood in the central laboratory Eurofins in the Netherlands. Blood samples for other exploratory biomarkers will be shipped to Eurofins for storage until analysis. Blood samples collection should be performed at screening and at SD28 after the last dose of rimeporide. Blood collection, on site preparation, handling and storage condition are described in the laboratory manual.

Plasma / Serum aliquots should must be stored on site in secured and controlled freezer until shipment for analysis. An alarm system and a samples rescue procedures must be available on site in case of excursion temperature.

All samples will must be shipped by an authorized carrier after completion of each study cohort to Eurofins central laboratory in the Netherland (Eurofins Central Laboratory, Bergschot 71 Bergschot 71, 4817 PA Breda, The Netherlands). The samples will be transferred in a container filled with enough dry ice to ensure that the samples are kept frozen. Temperature will be controlled over the shipment. Collection kits, shipment material and documentation (including dry ice) and a laboratory manual will be provided by the Sponsor before any patient inclusion in the study.
6.12 BLOOD SAMPLE VOLUMES

Biological samples collection have been defined in accordance with E6 & E11 ICH guidelines respectively related to Good Clinical Practice and clinical investigation of medicine products in the paediatrics population, EU directives 2001/83/EC, 2001/20/EC and GCP 2005/28/EC and CT 2001/20/EC. All activities will be fully in line with the respective national guidelines as well with the EU directives and guidelines listed above.

In particular blood will be withdrawn primarily to guide the safety review. Standard parameters (hematology, biochemistry) will be measured in each patient and urine will be tested routinely. The amount of blood that will be withdrawn during the study has been kept to a minimum and does not exceed 3% of the total blood volume within 4 week period and does not exceed 1% of total blood volume within 24 hours. These volume limits are set according to WHO recommendation for sample volumes in child health research.

Analysis done on blood samples will favour as much as possible the use of micro-sampling techniques. The volumes of blood to be drawn at each visit are about 56.5 ml over 8-10 weeks from screening to end of study visit (depending on your weight and medical condition).

- 11 ml of blood should be collected at screening visit (Vscr)
- 5 ml of blood should be collected at each of the following study visits, V2 (SD7), V3 (SD14), and V5 (EOS).
- Respectively 14.5 ml and 16 ml of blood should be collected at each of the following study visits. V1 (SD1) and V4 (SD28).

Additional samples may be required for safety reasons, if patient’s weight and health status allow the drawing of additional blood.

All blood samples will be drawn by the investigators or clinical research nurse. Painful procedures will be minimised by using indwelling catheters introduced under topical anaesthesia since repeated blood sampling is necessary during each visit.

All samples will be labelled with the subject’s unique study number only, ensuring anonymity.

7 OUTLINE OF STUDY PROCEDURES

Patients will be recruited from specialised study sites which are reference centres for DMD.

Analysis done on blood samples will favour as much as possible the use of micro-sampling techniques.

7.1 SCREENING

Patients and parents who agree to participate must sign the informed consent/assent form at the screening visit before any study procedures are performed.
Screening evaluations should be completed within 4 weeks prior to the first administration of study drug (SD1) as detailed below.

The following information must be collected and the following procedures must be performed:

- **Consent**
  - Signature of Informed Consent Form

- **Patient information:**
  - Demographic and medical history
  - Medications at screening
  - Date of DMD diagnosis and method used for diagnosis and results must be recorded
  - Treatment for DMD already received

- **Clinical Assessment:**
  - Vital signs: temperature (tympanic), respiratory rate, blood pressure and heart rate (supine and standing).
  - Physical and neurological examination, height (in cm) and weight (in kg)
  - 12-Lead Electrocardiogram: QT, QTcF, QTcB, PR, QRS duration and axis, Heart Rate.
  - Pulmonary Function Tests by spirometry (FEV1, FVC)
  - Echocardiography (LVEF)
  - 6-Minutes Walking Test

- **Local Laboratory tests**
  - Blood and urinary samples collection for safety hematology, biochemistry and urinalysis as described in section *Safety hematology, biochemistry and urinalysis.*

- **Exploratory parameters:**
  - Blood samples for centralised analysis as described in the *Pharmacodynamics Endpoints section.*

- **Other procedures**
  - Instruction for patient diary completion
  - Instruction for patient study card use
  - Instruction in case of new symptoms and changes of concomitant medication
  - Schedule the next study visits and NMRI (NMRS if applicable)

For each patient screened, an anonymized eligibility form must be sent by email to the Sponsor representative and medical advisor following the screening visit. This eligibility form summarizes the eligibility criteria, the concomitant medications, and the medical history. This form will be reviewed by the medical advisor to approve inclusion of each patient based on the screening data and to prevent protocol violations.
If the eCRF is available at this time, the eligibility confirmation will be performed based on the data recorded into the eCRF instead of the eligibility form. All the screening data must be immediately entered into the eCRF after screening visit to allow the review by the Medical advisor and to confirm the patient’s eligibility before his study day 1 (at least 48 hours are required for the medical advisor review).

7.2 NMRI (NMRS IF APPLICABLE) BEFORE FIRST DOSE AT STUDY DAY 1

Once Patient eligibility is confirmed, patients will undergo to Nuclear Magnetic Resonance Imaging (NMRI) (and Nuclear Magnetic Resonance Spectroscopy (NMRS) if applicable) to evaluate the skeletal/muscle structure at baseline.

NMRI procedures are detailed in the investigator manual. Only NMRI acquisition will be performed on site (Both NMRI and NMRS acquisitions will be performed for patients recruited in Paris). Anonymized (only study ID, subject ID and visit) imaging data will be uploaded into a secured platform according to ICH/GCP requirements for a central analysis.

7.3 STUDY DAY 1 (FIRST DOSE OF RIMEPORIDE)

7.3.1 Before rimeporide administration at Study Day 1 visit

7.3.1.1 Confirmation of patient eligibility at Study day 1

At study day 1 visit, the eligibility criteria including any AE, physical abnormalities, and changes in concomitant medications must be re-verified on day 1 by the investigator before confirming the eligibility of the patient and to administer the study drug (these tests, examinations and reviews must be repeated at SD1 even if they have been done the day before to prepare the IMP delivery. See section drug dispensing)

If the eligibility is confirmed on day 1, the study drug will be administered and the PK sampling profile will be automatically attributed via the eCRF as soon as investigator has confirmed the eligibility into the online platform.

If any eligibility criteria are no longer met on day 1 prior to intake of study medication, the patient will be considered as a screening failure and cannot continue to participate in the study. An End of Study visit will be performed instead.

The Investigator should keep a log of the patients pre-screened and screened for the study and reasons for non-eligibility, if applicable.
7.3.1.1 Baseline assessments at Study day 1

Patient should come at hospital under fasting condition (No food or fluid except water for 10 hours). A catheter will be placed and blood samples will be collected for local laboratory tests.

The following baseline assessments are conducted on SD1, before rimeporide is administered:

**Clinical assessments:**
- Vital signs: temperature (tympanic), respiratory rate, blood pressure and heart rate (supine and standing).
- Physical and neurological examination, including weight.

**Heart Function**
- 12-lead ECG Electrocardiogram: QT, QTcF, QTcB, PR, QRS duration and axis, Heart Rate.

**Local Laboratory tests:**
- Blood and urinary samples collection for safety hematology, biochemistry and urinalysis as described in the Safety hematology, biochemistry and urinalysis section.

**Pharmacokinetics:**
- A pre dose blood sample should be collected any time before the first administration of the study drug as described in the Pharmacokinetics Endpoints section.

**Other procedures**
- Patient diary review (Safety and compliance)
- AE and SAE review.
- Concomitant medication review.
- Study drug prescription and delivery.

7.3.2 First Rimeporide administration

A standard breakfast will be taken within 30 minutes before the first drug administration with no restriction on the kind of food or fluid given.

7.3.3 After first dose of rimeporide

The following assessments are conducted after the first dose of rimeporide

**Clinical assessments:**
- Temperature (tympanic), respiratory rate, blood pressure and heart rate (supine and standing) will be repeated at 1 hour, 2 hours and 4 hours after the first administration of study medication.

**Heart Function**
- 12-lead ECG Electrocardiogram will be repeated 1.5 hours after the dose.

**Pharmacokinetics:**
- Blood samples will be collected as described in the Pharmacokinetics Endpoints section.

**Procedures**
- Continuous AE and SAE review.
7.3.4 Second rimeporide administration
A standard lunch will be taken within 30 minutes before second drug administration with no particular restriction on the kind of food or fluid given.

7.3.5 After the Second dose of rimeporide
The following assessments are conducted after the second dose of rimeporide:

Clinical assessments:
- Temperature (tympanic), respiratory rate, blood pressure and heart rate (supine and standing) will be repeated at 1 hour, 2 hours and 4 and 6 hours after the second administration of study medication.
- A12-lead ECG will be recorded 1.5 hours after the dose.

Pharmacokinetics:
- Blood samples will be collected as described in Pharmacokinetics Endpoints section.

Procedures
- Continuous AE and SAE review

Patients will be kept under observation for at least 6 hours after the second dose of study medication. Prior to leaving the study site at the end of the visit, the patient must be reviewed by the investigator or other study physician along with the clinical and safety assessments and ECGs. If there are no safety concerns, the patient may go home accompanied by his parents or guardian after this period. In the event of any safety concerns the patient will be asked to stay overnight on site and additional safety observations made as clinically indicated.

Before leaving the hospital, the patient/parent or guardian will receive the instruction for the administration of rimeporide at home and a patient diary will be provided, which will help to track any deviation of compliance and to collect information about adverse events. Patients will also receive a “patient study card” that they should carry with them at all times during the treatment period. Study title, details of the study drug and phone number to call in case of emergency will be recorded in the card. A general practitioner letter will also be provided to be given to the patient’s family doctor for information about participation of his/her patient to the study.

7.4 WEEK 1 (DAY 7 +/- 2 DAYS)
At study day 7 +/- 2 days, patient will go back to the hospital for a safety visit.
The following assessments are conducted:
Clinical assessments:
- Vital signs: temperature (tympanic), heart and respiratory rate, blood pressure (supine and standing).
- Physical and neurological examination including weight.

Heart Function
- 12-lead ECG Electrocardiogram.

Local Laboratory tests:
- Blood and urinary samples collection for safety hematology, biochemistry and urinalysis as described in Safety hematology, biochemistry and urinalysis section.

Other Procedures
- Patient diary review (Safety and compliance)
- AE and SAE review.
- New concomitant medication or new medication changes review.
- Study drug prescription and delivery

7.5 Week 2 (Day 14 +/- 2 days)
At study day 14 (or week 2) patient will go back to the hospital safety visit.
The following assessments are conducted:

Clinical assessments:
- Vital signs: temperature (tympanic), respiratory rate, blood pressure and heart rate (supine and standing).
- Physical and neurological examination, including weight.

Heart Function
- 12-lead Electrocardiogram.

Local Laboratory tests:
- Blood and urinary samples collection for safety hematology, biochemistry and urinalysis as described in Safety hematology, biochemistry and urinalysis section.

Other Procedures
- Patient diary review
- AE and SAE review.
- New concomitant medication or new medication changes review.
- Drug accountability of returned study treatment.
- Study drug prescription and delivery

7.6 Week 3 (Day 21 +/- 2 days)
A phone call will be made to check that the drug has been properly taken, discuss the clinical conditions of the patient, and note any possible adverse event or new medication reported by the patient or his parents. An unplanned visit may be scheduled if the patient needs to be assessed or treated for any clinical condition described during these phone calls or requires more examination in the opinion of the investigator (see unscheduled visit section).
7.7 **NMRI (NMRS IF APPLICABLE) AT DAY 27 (+/-2 DAYS) OF THE STUDY**

Just before the end of treatment, at Day 27 +/- 2 days of the treatment, patients who have agreed to this optional procedure will undergo a new local NMRI (and NMRS for patients recruited in Paris). NMRI procedures are detailed in the investigator manual. Only NMRI acquisition will be performed on site (Both NMRI and NMRS acquisitions will be performed on patients recruited in Paris). Anonymised (only study ID, subject ID and visit) imaging data will be uploaded into a secured platform according to ICH/GCP requirements for a central analysis.

7.8 **WEEK 4 (DAY 28 +/- 2 DAYS)**

At study day 28 (or week 4) patient will go back to the hospital for the clinical and laboratory assessments and to return the unused study drug and the drug diary where drug assumption has been recorded.

Patient should come at hospital under fasting condition (No food or fluid except water for 10 hours) for local laboratory tests. Immediately after blood sample collection, a moderate fat breakfast will be taken within 30 minutes before the last drug administration of the study with no restriction on the kind of food or fluid given.

Then the following assessments will be performed:

- **Clinical assessments**: Vital signs: temperature (tympanic), respiratory rate, blood pressure and heart rate (supine and standing).
- **Heart Function**: 12-lead ECG Electrocardiogram 1.5 hours after last rimeporide dose.
- **Local Laboratory tests**: Blood and urinary samples collection for safety hematology, biochemistry and urinalysis as described in Safety hematology, biochemistry and urinalysis section.
- **Pharmacokinetics**: Blood samples will be collected as described in Pharmacokinetics Endpoints section. Blood samples will be taken in the following time frames: (0.5 – 1h), 6h after the last dose of rimeporide.
- **Pharmacodynamics/Exploratory parameters**: Blood samples centralised analysis as described in Pharmacodynamics Endpoints section any time after last dose of rimeporide.
- **Procedures**: Patient diary review
- AE and SAE review/New concomitant medication or new medication changes review.
Drug accountability of returned study treatment.

6 hours after the last rimeporide administration, patient may go home with you unless the study doctor advises otherwise.

7.9 END OF THE STUDY VISIT (1-2 WEEKS +/- 2 DAYS POST LAST RIMEPORIDE DOSE)

This will be last visit of the study and identified as end of study follow-up visit. Patient will undergo clinical and laboratory assessments and to return the unused study drug and the drug diary where drug assumption has been recorded.

The following assessments will be performed:

**Clinical assessments:**
- Vital signs: temperature (tympanic), respiratory rate, blood pressure and heart rate (supine and standing).
- Physical and neurological examination including weight.

**Heart Function:**
- 12-lead ECG Electrocardiogram.

**Local Laboratory tests:**
- Blood and urinary samples collection for safety hematology, biochemistry and urinalysis as described in Safety hematology, biochemistry and urinalysis section.

**Procedures**
- Patient diary review.
- AE and SAE review.
- New concomitant medication or new medication changes review.
- Drug accountability of returned study treatment.

7.10 WITHDRAWAL VISIT (1-2 WEEKS +/- 2 DAYS AFTER DECISION)

The same assessment procedures should also be followed by the Investigator for any patient who is withdrawn prematurely from the study within 1-2 weeks after the decision to withdraw is made. For any withdrawal from the study as a result of investigator’s decision, patient’s decision or the decision of their parent/guardian, patient will go back to the hospital for a last visit on site. Clinical and laboratory assessments will be performed and unused study drug, drug diary where drug assumption has been recorded must be returned. Investigator should ask them and patient’s parent / guardian any relevant information regarding their clinical conditions, note any possible adverse event or new medication to be reported.
Patient will undergo to the following clinical and laboratory assessments:

**Clinical assessments:**
- Vital signs: temperature (tympanic), respiratory rate, blood pressure and heart rate (supine and standing);
- Physical and neurological examination, including weight;

**Heart Function:**
- 12-lead ECG Electrocardiogram.

**Local Laboratory tests:**
- Blood and urinary samples collection for safety hematology, biochemistry and urinalysis as described in Safety hematology, biochemistry and urinalysis section.

**Procedures**
- Patient diary review
- AE and SAE review.
- New concomitant medication or new medication changes review.
- Drug accountability of returned study treatment.

No other specific assessments are required unless needed to follow-up an ongoing AE/SAE. Patients who are withdrawn due to a serious adverse event (SAE) should be followed-up until the resolution of the event or until the outcome of the event is known and stable. Any withdrawal of enrolled subjects from the trial must be reported and explained on the eCRF.

Patients and parents should be asked if they are willing to continue the study without study treatment. In this case, they should come back to the hospital for all subsequent study visits to be followed by the investigator and to perform the study tests and the examination as initially planned.

Patients and parents/ legal guardian who do not agree to continue study visits without study treatment must be asked whether they agree that all data collected so far could be used for the analysis. Also, they must be asked whether they agree that biological samples collected so far could be kept and stored in the secured place for further analysis.

### 7.11 ASSESSMENTS IN CASE OF UNPLANNED (UNSCHEDULED) VISITS

Unplanned visits may occur should the patient need to be assessed or treated for any clinical condition that arises during the study. This may include the evaluation and follow-up of AEs, SAEs or laboratory tests. The following assessments (as detailed in the Schedule of Assessments) should always be performed at minimum, but additional assessments may be added according to the clinical judgment of the Investigator.

In case the patient is still on treatment period during the unscheduled visit the following assessments will be performed:
Clinical assessments:
- Vital signs: temperature (tympanic), respiratory rate, blood pressure and heart rate (supine and standing).
- Physical and neurological examination, including weight.

Heart Function
- 12-lead ECG Electrocardiogram.

Local laboratory tests:
- Blood and urinary samples collection for safety hematology, biochemistry and urinalysis as described in Safety hematology, biochemistry and urinalysis section.

Procedures
- Patient Diary
- AE and SAE review.
- New concomitant medication or new medication changes review.
- Drug accountability of returned study treatment.

8 SAFETY PROCEDURES

The collection and reporting of Adverse Events (AEs) will be in accordance with EU Directive for Clinical Trials 2001/20/EC and the Detailed Guidance on the Collection, Verification and Presentation of Adverse Events/Reaction Reports Arising From Clinical Trials of Medicinal Products For Human Use (‘CT-3’).

8.1 DEFINITION

8.1.1 Adverse events

Adverse events (AEs) are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product. All adverse events (AEs) reported spontaneously by the patients or his relatives or observed by the Investigator or his staff during the clinical study up to and including the end-of-study visit will be reported on the AE data collection form. It is the Investigator(s) responsibility to assess each AE. This may be delegated to other suitably qualified physicians in the research team who are trained in recording and reporting AEs. Each AE must be assessed for seriousness, causality and severity and expectedness. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the patient’s medical records - source data) with reference to the investigator brochure.

All AEs will be captured in the appropriate eCRF section. All AEs occurring while a patient is participating in the study must be documented appropriately, regardless of causal relationship. All AEs will be followed to adequate resolution, whenever possible.
Any medical condition that is present at the time that the patient is screened will be considered as baseline and not reported as an AE. However, if it deteriorates at any time during or following administration of the first IMP infusion, it will be recorded as an AE. For all AEs, the following will be assessed and recorded in the eCRF: the onset, the end of the AE, the description of the AE, intensity, and relationship to Investigational Medicinal Product (IMP), action taken regarding IMP, any treatment received and outcome to date.

**The intensity of the AE:**

Intensity of adverse events will be graded on a three-point scale using the following definitions:

- **Mild:** Discomfort noticed but no disruption of normal activity
- **Moderate:** Discomfort sufficient to reduce or affect normal daily activity
- **Severe:** Inability to work or perform normal daily activity.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event, at each level of intensity, to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

**The outcome of the AE:**

The outcome should be documented in the eCRF according to the following definition:

- **Recovered:** AE disappeared
- **Not yet recovered:** AE is still existing, or patient is recovering
- **Alive with sequelae:** AE results in permanent disability / incapacity
- **Death:** patient died
- **Unknown:** only if patient was lost of the follow-up

**Causality to the IMP:**

The Investigator should make an assessment of whether the AE is likely to be related to the IMP according to the following definitions.

- **Unrelated:** a relationship to the study medication can be definitely ruled out (reasonable explanation must be given; eg involved in traffic accident while in back seat of car)
- **Unlikely:** a relationship to the study medication is considered unlikely: the time relationship to the administration of study medication does not suggest a causal relationship and/or the underlying disease, other concomitant illnesses or medications appear more likely explanations according to present knowledge;
- **Possibly related:** there is a reasonable possibility that the adverse event may have been caused by the study medication: there is a reasonable time relationship to the administration of study
medication but the nature of the event, the underlying disease, and/or concomitant medication or concomitant illnesses suggest that other explanations are a significant possibility

- **Probably related:** the study medication is considered to be the most likely cause of the adverse event: there is a reasonable time relationship to the administration of the study medication and the event is considered unlikely to be or cannot be attributed to concurrent disease or concomitant medications.

All AEs assessed as having a reasonable suspected causal relationship to the IMP (i.e. possibly, probably) will be considered as related to the IMP for regulatory reporting purposes.

**Seriousness:**
The Investigator should make an assessment of seriousness as defined below:

### 8.1.2 Serious Adverse Events
A serious adverse event (SAE) is any untoward medical occurrence that:

- results in death (note: death is an outcome, not an event);
- is life-threatening; (note: the term "life-threatening" refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe);
- requires in-patient hospitalization or prolongs an existing hospitalization;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above (note: examples are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization).

### 8.1.3 Abnormal Laboratory Test Values
All safety laboratory tests (haematology and blood biochemistry), for each visit time-point, should be captured in the database from the local laboratory. Abnormalities should be coded as clinically significant or not clinically significant. Clinically significant changes in laboratory values should also be reported as adverse events, however, if a laboratory abnormality leads to diagnosis of a new clinical event (e.g.: a high white blood cell count leads to a diagnosis of leukaemia) the clinical diagnosis should be reported on the AE form, not the laboratory abnormality leading to the diagnosis.
8.2 REPORTING PROCEDURES

AE defined as serious which require reporting as an SAE should be reported to Sponsor or its delegate immediately. The term severe is a measure of intensity/severity: thus a severe adverse event is not necessarily serious. For example, nausea of several hours’ duration may be rated as severe, but may not be clinically serious.

For the purpose of this study, the following will not be considered as serious adverse events:

- Elective hospitalizations or surgical procedures that are a result of a patient’s pre-existing condition(s) which have not worsened since receiving IMP. Such events should still be recorded as adverse events in the eCRF
- Any serious clinical adverse event or clinically significant abnormal laboratory test value that occurs during the course of the study, must be communicated by the Investigator to the Sponsor or its delegate, by fax or electronic transmission, within 24 hours of awareness.

On becoming aware that a patient has experienced an SAE, the investigator (or delegate) must complete, the study specific SAE, report form with all available case details concerning the patient, and the event, date and sign the SAE report form. The SAE report form should be faxed to pharmacovigilance responsible person for the trial, using one of the number listed below and no later than 24 hours after first becoming aware of the event:

Contact information for SAE reporting: Jennie Moore  
Phone number: + 44 (0) 1963 350862  
Fax: + 44 1908 251 499  
E-mail: jmoore@qed-clinical.com

Original and copies of SAE forms, and all related safety documentation and correspondence must be filed in the ISF.

For SAE report form completed by someone other than the investigator, the investigator will be requested to countersign the original SAE form to confirm the causality and the severity assessments. The SAE report form should be returned to pharmacovigilance responsible person for the trial and a copy filed in the ISF.

Investigators should also report SAEs within their own institution in accordance with local practice.

8.2.1 Suspected Unexpected Serious Adverse Reactions Reporting

On receipt of an SAE Form, seriousness and causality will be determined independently by the Medical Monitor of the study. An SAE judged by the investigator and/or Medical Monitor to have a causal
relationship (possible or probable) with the trial medication will be regarded as a Serious Adverse Reaction (SAR).

The Medical Monitor will assess all SARs for expectedness according to the reference document as defined in the current version of the investigator's brochure. If the event meets the definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR); that is unexpected (i.e. not defined in the current version of the IB), related to study drug and serious, it will be classified as a SUSAR.

Unexpected adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

These reactions are SUSARs if the following three conditions are met:

1. the event must be serious;
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. unexpected against the current version of the Investigator Brochure.

**Fatal or life-threatening SUSARs**

All competent authorities and the Ethics Committees of participating countries will be notified as soon as possible in writing (CEC) / electronically (CA) but no later than 7 calendar days after the sponsor or delegate has first knowledge of the minimum criteria for expedited reporting. In each case relevant follow-up information should be sought and a report completed as soon as possible. It will be communicated to the competent authorities and the Ethics Committees within an additional eight calendar days.

**Non fatal and non life-threatening SUSARs**

All other SUSARs and safety issues, must be reported to all the competent authorities and the Ethics Committees of participating countries as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting.

Sponsor or its delegate will report all SUSARs to the EMA's EudraVigilance database within 15 days, as well as to the relevant National Competent Authorities when required.

In case of incomplete information at the time of initial reporting, all the appropriate information for an adequate analysis of causality should be actively sought from the reporter or other available sources. The sponsor will report further relevant information after receipt as follow-up reports.

The sponsor shall inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of subjects. Details of all SUSARs and any other safety issue arises during the trial will be reported to Principal investigators. A copy of any such correspondence should be filed in the ISF.
8.2.2 Provision of follow-up information
Patients should be followed up until resolution of the event.
Follow up information should be provided on a new SAE form. Relevant follow-up information on SAEs should be forwarded to Sponsor or its delegate as soon as it becomes available. In addition, the Investigator must be available to answer without delay any request for follow-up information or questions Sponsor or its delegate may have regarding the SAE.
Relationship to the study drug will be established by the Investigator in order to define the need for expedited reporting.

8.2.3 Reporting period
Details of all AEs and SAEs will be documented and reported from the date of commencement of protocol defined treatment until 15 days after the administration of the last treatment.

8.2.4 Post study SAEs and SUSARs:
SAEs that are judged to be at least possibly related to the IMP and unexpected must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

8.2.5 Development Safety Update Report (DSUR)
In addition to the expedited reporting, sponsors will submit a Development Safety Update Report (DSUR) once a year throughout the clinical trial (from the date of the first clinical trial competent authority approval received for the trial to the submission to the end of the trial declaration) or on request a safety report to the competent authority and the Ethics Committee of the concerned participating countries, taking into account all new available safety information produced during the reporting period.
Sponsor or delegate will include details of all SAEs, SUSARs and adverse events reactions will be reported to competent authorities on request.

8.3 FOLLOW-UP OF SAFETY PARAMETERS

8.3.1 Treatment and Follow-up of Adverse Events
All Adverse events, should be followed-up until the event has returned to baseline status or has stabilised. If a clear explanation is established, it should be recorded on the CRF.
All SAEs must be followed-up until the event has either resolved or reached a stable clinical outcome.
8.3.2 Follow-up of Abnormal Laboratory Test Values
In the event of unexplained clinically relevant abnormal laboratory test values, the tests should be repeated immediately and followed-up until the values have returned to within normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established, it should be recorded on the eCRF.

8.3.3 Pregnancy
Considering the age of the study patients (up to 14 years) the usual concerns in clinical trials concerning pregnancy in partners are less prominent. However, in the unlikely event of pregnancy occurring in partners of male enrolled patients, it must be reported to Sponsor or its delegate within 24 hours of awareness. All information pertaining to the pregnancy should be reported using the Sponsor Pregnancy form. Pregnancies should be followed until conclusion to obtain outcome information and reported using a pregnancy follow up report.

8.4 SAFETY MONITORING COMMITTEE
An independent Safety Monitoring Committee (SMC) composed of relevant Experts including 3 physicians of which at least one is experienced in the management of patients with Duchenne Muscular Dystrophy, and a pharmacologist specialized in paediatrics will review safety data during the study. The procedures of the SMC will be documented in a separate charter.

The safety monitoring committee will meet at least 4 monthly to review overall safety in the study as well as at the end of each cohort to recommend whether the dose can be escalated as planned. After each meeting a recommendation to continue the study without modification, continue with modifications or discontinue the study will be made. In addition the safety monitoring committee will review SAEs on an ongoing basis and will hold additional meetings as needed to discuss these and make corresponding recommendations.

9 STOPPING RULES
The subsequent sections are based on the following AE grading:

- Grade I: Mild intensity
- Grade II: Moderate intensity:
- Grade III: Severe intensity:

9.1 STOPPING OR SUSPENSION OF DOSING AT THE INDIVIDUAL PATIENT LEVEL
Dosing will be suspended at the individual level until evaluation by the medical monitor:
• If a SAE considered related (possibly and probably) to study medication is observed;
• In the case of adverse reactions of moderate intensity (grade II) persisting for more than 2 weeks or of severe intensity (grade III) until full evaluation by the SMC;
• In the case of adverse reactions of shorter duration or lower intensity if the investigator considers this clinically indicated;

Each such case will be evaluated by the medical monitor in communication with the investigator. The medical monitor will inform the SMC about the events in a timely manner.

9.2 STOPPING OR SUSPENSION OF DOSING AT THE STUDY LEVEL

9.2.1 Non Serious Adverse Events:
Dosing will be interrupted at the study level to allow for review of cumulative safety data by the SMC if any of the following conditions are met:

• ≥2 severe AEs or ≥3 moderate AEs considered to be possibly/probably or definitely related to investigational drug product;
• ≥2 moderate AEs (grade II) considered to be possibly/probably or definitely related to investigational drug product and intensity persisting for more than 2 weeks;
• When 2 or more patients develop 2 consecutive Cystatin C levels ≥ 2 folds their respective average pre-treatment values;
• When 2 or more patients develop a confirmed unexplained proteinuria of > 2+;
• Any unexplained Gamma GT > 3 fold the upper limit of normal (ULN) in combination with bilirubin ≥2 fold the ULN.

9.2.2 Serious Adverse Events (SAE):
All SAEs will be reported to and reviewed by the SMC an ongoing basis.
Dosing will be interrupted at the study level to allow for review of cumulative safety data by the SMC if any SAE considered to be possibly/probably or definitely related to investigational drug product

9.3 SUSPENSION OF DOSE ESCALATION
If at any individual dose level, one SAE, or severe AE, or moderate AE lasting more than 2 weeks considered possibly/probably or definitely related to investigational drug product occurs at a particular dose level the SMC will decide whether dosing can proceed at the next higher dose or whether a further 5 patients should be added at the same dose level.
10 STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

Full details of all statistical issues and planned statistical analyses will be specified in a separate Statistical Analysis Plan (SAP), which will be finalised prior to the locking of the study database. This section contains an overview of the planned methods of analysis.

10.1 SAMPLE SIZE

A sample size of 20 evaluable patients has been selected for this pilot study, based on practical considerations, since this is an exploratory study and not a confirmatory trial. Additional 5 patients might be included in case safety allow to further escalate the dosage. Due to the rarity of DMD patients the recruitment is competitive across all sites in order to gather data in a reasonable timeframe, anticipated to be about 12 months.

10.2 ANALYSIS SETS

All analysis sets will be defined prior to final database closure. In addition to the analysis sets listed below, further exploratory analyses may be performed using other subgroups of patients.

10.2.1 Safety Analysis Set

The safety analysis set will include all patients who receive at least one dose of study drug.

10.2.2 Intent-to-Treat Analysis Set

The intent-to-treat (ITT) analysis set will include all patients who receive at least one dose of study drug and will be used for PK/PD analyses.

10.3 STATISTICAL AND ANALYTICAL METHODS

As this is an exploratory study, statistical methods will focus on summarising the data collected using appropriate graphical and tabular presentations. For measurements of continuous endpoints, summary statistics will include n, mean, median, standard deviation, minimum and maximum values. For binary data the numbers and percentages will be tabulated and 95% confidence intervals will be derived. All endpoints are considered to be exploratory in this study, and no hierarchy of endpoints has been specified, as the objective in terms of efficacy data is to inform the planning of formal efficacy studies of rimeporide.

10.3.1 Safety Data

All data relating to safety will be listed and summarised using descriptive statistics. AEs will be coded according to MedDra and tabulated by body system and by preferred term for each dose level. AEs will also be tabulated by severity and relationship to the study medication.
Summaries will also be produced of SAEs, and AEs leading to withdrawal from the study.

For each clinical laboratory test, individual patient values will be listed and summarised and change from pre-treatment baseline values calculated and summarised. Any values outside the standard reference range will be flagged. Summaries of marked abnormalities and shift tables will be tabulated for each laboratory test by dose level.

In addition, other exploratory analyses of safety data, including summaries for different subsets of patients, may be conducted.

10.3.2 Pharmacodynamics Data

All PD data will be summarised using appropriate graphical and tabular presentations.

Descriptive statistics (N, arithmetic means, SD, geometric means, geometric CV, medians, Min and Max) will be presented for all pharmacokinetic/pharmacodynamics parameters, separately for each dosage level.

In addition, other exploratory analyses of pharmacodynamics endpoints, including summaries for different subsets of patients, may be conducted.

10.3.3 Missing Data

No imputations of missing data will be performed.

10.4 REPLACEMENT POLICY

10.4.1 For Patients

Any patient withdrawn from the study for reasons other than safety or tolerability concerns will be replaced.

10.4.2 For Centres

A centre may be replaced for the following administrative reasons: excessively slow recruitment, poor protocol adherence.

11 DEFINITION OF THE END OF THE STUDY

The end of the study will take place at the date of the last visit of the last patients enrolled in the study.

The EUDRA CT Declaration of the End of Trial form should be sent to the CAs and relevant ECs within 90 days of the end of the trial, or within 15 days if the project is terminated early. Where the project is terminated early, or halted temporarily, reasons will be given.
A summary of the End of Trial Study Report should be sent to the CAs and relevant Ethics Committees within 12 months of the end of the trial. The summary of the final report may be enclosed with the end of study declaration, or sent to the CAs and relevant ethics committees subsequently. All correspondence with the CAs and ECs will be retained in the Trial Master File.

PART II

12 ETHICAL AND LEGAL ASPECTS

12.1 GOOD CLINICAL PRACTICE
Study implementation and conduct will be done in full compliance with existing national legislation and EC directives and rules on ethical issues that are relevant to the project. Sponsor and its delegates will comply with the international conventions and codes of conduct, and in particular with the Helsinki Declaration of the World Medical Association adopted by the World Medical Assembly. Respect for human rights and fundamental freedoms is enshrined in the Treaty on European Union as in Article 6 of the Treaty on European Union as amended by the Treaty of Amsterdam, enforced on 1 May 1999. They will also take into account the declaration of the EU Clinical Trials Directive (2001/20/ec), ICH Topic E 6 (R1) “Guideline for Good Clinical Practice” (CPMP/ICH/135/95/Step5), the following Regulation (EU) No 536/2014 of the EUROPEAN PARLIAMENT and of the COUNCIL of 16 April 2014, that will become applicable, no earlier than 28 May 2016; the opinions of the European Convention on Human Rights and Biomedicine of the Council of Europe; the directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001the Council Directive of 24 November 1986 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the protection of animals used for experimental and other scientific purposes (86/609/EEC).

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local site specific approval. This does not affect the individual clinicians’ responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

12.2 RESPONSIBILITIES
The Investigator shall ensure that the clinical study is performed in accordance with the protocol, the Declaration of Helsinki, the guidance on Good Clinical Practice and the regulatory requirement in force in the participating country concerned.

The investigator shall ensure that all persons assisting with the trial are appropriately qualified and adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.
The investigator shall ensure to maintain in an investigator study file, all essential documents which reflect the conduct of the trial and is therefore a key element in trial reconstruction. The site file should be established at the beginning of the trial, be rigorously maintained and available at any time for monitoring, audit or inspection purposes. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

ISF should be established at the beginning of the trial. A final close-out of a trial can only be done when the monitor has reviewed ISF and confirmed that all necessary documents are in the appropriate files.

The following documents should be generated and should be on file before the trial formally starts:

- Investigator brochure and Investigator’s brochure updates to document that investigator is informed in a timely manner of relevant information as it becomes available.
- Signed protocol and amendments, if any, and sample case report form
- Informed consent form (including all applicable translations)
- Any other written information to document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent
- Any revision of trial related documents that take effect during trial (protocol/amendment(s) and case report form, informed consent form any other written information provided to subject)
- Financial aspects of the trial to document the financial agreement between the investigator/institution and the sponsor for the trial.
- Insurance statement to document that compensation to subject(s) for trial-related injury will be available.
- Signed agreement between involved parties,
- Dated, documented favourable opinion of Ethics Committee for initial submission and subsequent amendment(s) and/or revision(s)
- Ethics committee composition to document that the Ethics Committee is constituted in agreement with Good Clinical Practice.
- Regulatory authority (ies) authorisation/approval/notification of protocol to document appropriate authorisation/approval/notification by the regulatory authority (ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s).
- Regulatory authority (ies) authorisation subsequent amendment(s) and/or revision(s) if any.
- Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and/or supporting trial staff to whom investigator tasks are delegated to document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects.
Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol to document normal values and/or ranges of the tests according to the state of the art.

Updates to normal value(s)/range(s) for medical/laboratory/technical procedure(s)/test(s) included in the protocol to document normal values and ranges that are revised during the trial.

Medical/laboratory/technical procedures/tests to document competence of facility to perform required test(s), and support reliability of results (Certification or accreditation or established quality control and/or external quality assessment or calibration or other validation).

Updates of medical/laboratory/technical procedures/tests to document that tests remain adequate throughout the trial period.

Instructions for handling of investigational medicinal product(s) and trial related materials to document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational medicinal products and trial-related materials.

Distribution records for investigational medicinal product(s) and trial related materials to document distribution dates, batch numbers and method of distribution of investigational medicinal product(s) and trial-related materials. To allow tracking of product batch, review of distribution conditions, and accountability.

Certificate(s) of analysis of investigational product(s) to document identity, purity, and strength of investigational medicinal product(s) to be used in the trial.

Investigational medicinal product(s) accountability at site to document that the investigational medicinal product(s) have been used according to the protocol. To document the final accounting of investigational medicinal product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor.

Documentation of investigational product destruction to document destruction of unused investigational products by sponsor.

Monitoring visit reports to document site visits by, and findings of, the monitor.

Relevant communications other than site visits to document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting, letters, meeting notes, notes of telephone calls.

Signed informed consent forms to document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission.

Source documents to document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject.

Signed, dated and completed case report forms to document that the investigator or authorised member of the investigator’s staff confirms the observations recorded.
- Documentation of case report form corrections to document all changes/additions or corrections made to case report form after initial data were recorded
- Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and Ethics Committees of suspected unexpected serious adverse reactions and of other safety information
- Notification by sponsor to investigators of safety information in accordance with ‘The detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use
- Annual Safety reports to Ethics Committees and authority(ies)
- Subject screening log to document identification of trial subjects who entered pre-trial screening. The Investigator is responsible for keeping a record of all patients (or their legally authorised representative) who sign an informed consent document and are screened for entry into the study. Patients who fail screening must have the reason(s) recorded in their source documents and the study-screening log.
- Subject identification code list to document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time.
- Subject enrolment log to document chronological enrolment of subjects by trial number.
- Investigational medicinal product accountability at the site to document that investigational medicinal product(s) have been used according to the protocol.
- Record of retained body fluids to document location and identification of retained samples.
- Audit certificate
- Final trial close-out monitoring report to document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files.
- Final report by investigator to Ethics Committees where required, and where applicable, to the regulatory authority (ies) to document completion of the trial.
- Clinical study report to document results and interpretation of trial.

Essential documents should be complete, legible, accurate, and unambiguous. They should be signed and dated as appropriate.

### 12.3 CONSENT

The paediatric population represents a vulnerable subgroup. Special measures have been taken to correctly inform them, to protect their rights and to shield them from undue risk.

It is the responsibility of the Principal investigator or co-investigator, to obtain written informed consent from the patient’s parents or legal guardian and assent from each patient prior performing any trial related procedure.
As a rule, a paediatric subject is legally unable to provide informed consent. Consequently, paediatric study participants are dependent on their parent(s)/legal guardian to assume responsibility for their participation in clinical studies. Fully informed consent should be therefore obtained from the legal guardian in accordance with regional laws or regulations. All participants will be informed to the fullest extent possible about the study in language and terms they are able to understand. An informed consent and assent documents that includes both information about the study and the consent form will be prepared and given to the patient and parents/legal guardian respectively. A parents/legal representative information sheet (PIS) together with an informed consent form (ICF) and an assent form where appropriate (age of assent to be consistent with local legal requirements) will be provided to them to explain the study, the study’s procedures (not limited to invasive, painful procedures), Procedures to prevent or limit physical discomfort, the potential risk and benefit of participating in the study, and their rights. This document will contain all ICH, GCP, and locally required regulatory elements (whichever is more stringent).

A PIS will be provided to each patient to make sure they have understood and agreed to take part in the study; two PIS will be available, one for the age ranges of 6 to 10 years old and one for 11 to 14 years old. The language used will be based on the maturity of the child and their ability to understand the study procedure. Age-appropriate explanation will be given to the child prior to any investigation or procedure, in order to decrease anxiety and anticipation of pain, in honest, but not frightening terms.

The patients and parents / legal guardians should be given sufficient time to read the Patient information sheet and to discuss their participation with others outside of the site research team if they wish do. Investigators must ensure that they had adequately explain the aim, trial treatment, trial procedures and examinations, and anticipated potential hazards of taking part in this trial to the patient, parents / legal guardians. Medical and study staff will take all the time necessary to correctly explain what it will happen during the examinations. The patient and/or parent/legal guardian must be given an opportunity to ask any they might have. Patient recruitment will be performed in a manner free from inappropriate inducements either to the parent(s)/legal representative or to the study participant.

The investigator should also stress that the patient and/or parents/legal guardians are completely free to refuse to take part or withdraw from the trial at any time. The right of the patient and/or parent/legal guardian to refuse to participate in the trial without giving a reason must be respected.

Information to patients will be split into a Patient Information Sheet that provides detailed information about the trial and its benefits and risks, and the Informed Assent/Consent Form that is used to obtain the dated signature from the patient as evidence of the patient’s agreement to partake in the study. Since the patients in the study are minors, written assent must be obtained from the minor wherever it is possible to do so (as appropriate according to age and national legislation). If patient and parents/legal guardian (as mandated by local rules: individual or judicial or other body authorised under applicable law to consent on behalf of a prospective patient to the patient’s participation in the procedures involved...
in the research) agree their child to participate in the trial, they should be asked to sign and date the latest version of informed consent form. Both parents must signed the informed consent form unless one parent is not legally allowed to sign.: Permission of one parent is sufficient if the other parent is deceased, unknown, incompetent, not reasonably available, or does not have legal responsibility for the care and custody of the minor child. The investigator must then sign and date the form on the same day as the parent/legal/guardian.

PIS and ICF will be prepared based on local requirements and law, cultural specifications, and approved by an Ethical Committee. The modalities for obtaining informed consent from the parents and Assent from the minor will be defined at the site initiation visit and documented in the clinical trial centre in the Investigator Site File (ISF). A copy of the signed ICF should be given to the patient and/or parent/legal guardian, another signed copy should be filed in the patient’s medical records, and the original placed in the Investigator Site File (ISF).

Details of the informed consent discussions should be recorded in the patient’s medical records; this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the PIS and ICF. Throughout the trial, the patient and/or parent/legal guardian should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient’s continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient, in which case the process above should be followed and the patient’s right to withdraw from the trial respected. If an amended protocol impacts the content of the informed consent document, the consent and assent documents must be revised and the patient and parent/legal guardian must again give written assent/informed consent respectively. Patients already participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. A copy of the revised informed consent and assent documents must be given to the parents or guardians. The Investigator will retain the original signed updated consent document in ISF. A copy of the signed ICF should be given to the patient and/or parent/legal guardian, another signed copy should be filed in the patient’s medical records.

With the patient’s prior consent, their medical practitioner should also be informed that they are taking part in the trial.

12.4 SUBJECT COMPENSATION

Patients and their parents or guardians will not receive compensation for taking part in the study but will receive reimbursement for reasonable travel and accommodation costs associated with their participation.
12.5 ARCHIVING
ISF must be retained securely prior to archive and then archived for sufficient periods to allow for audit and inspection by regulatory authorities and should be readily available upon request.

To comply with international regulations, the records should be retained by the investigator for 15 years or longer in accordance with national regulations after the end or termination of the trial, or 2 years after the marketing authorization or the sponsor has discontinued its research with respect to such drug. The investigational sites must notify the sponsor in writing before destroying any data or records.

Storage conditions should ensure that essential records are maintained in a legible condition and can be retrieved upon the request of a regulatory authority. Any change in the location of the stored documentation should be recorded in order to allow tracking. Adequate and suitable space should be provided for the secure storage of all essential records from completed studies. The facilities should be secure, with appropriate environmental controls and adequate protection from physical damage.

The investigator is recommended to make the sponsor aware of the storage arrangements for their essential documents. The ultimate responsibility for the documents to be retained by the investigator/institution resides with the investigator/institution. If the investigator becomes unable to be responsible for their essential documents (e.g. relocation, retirement etc) the sponsor should be notified in writing of this change and informed as to whom the responsibility has been transferred. Details of these arrangements should be documented in the clinical trial centre TMF.

12.6 CONFIDENTIALITY AND DATA PRIVACY

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the relevant data protection legislation in the member state.

Patients will be identified using only their unique trial number.

Sponsor affirms the patient's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is more stringent). Sponsor requires the Investigator to permit sponsor representatives (Monitor) and when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws (any copies of patients' records must be duly anonymised to protect patients' confidentiality).

Should direct access to medical records require a waiver or authorisation separate from the patient’s statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual. Representative of the sponsor may be required to have access to patients medical records for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

Representative of sponsor must maintain the confidentiality of all patient’s data and will not disclosed information by which patients may be identified to any third party other than those directly involved in the treatment and organization for which the patient has given explicit consent for data transfer.
12.7 PROTOCOL AMENDMENTS

Substantial amendments will be submitted to the IEC for written approval and where applicable to National Competent Authorities. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IEC should specifically reference the Principal Investigator’s name, protocol number, study title and amendment number(s) that is/are applicable.

12.8 APPROVAL OF THE CLINICAL STUDY PROTOCOL AND AMENDMENTS

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IEC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

Sponsor can only supply study drug to an Investigator after sponsor or their authorised representative, an international CRO, has received documentation on all ethical and legal requirements for starting the study. This documentation must also include a list of the members of the IEC and their occupation and qualifications. If the IEC will not disclose the names of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. Formal approval by the IEC should preferably mention the study title, study code, study site, and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member (chairman or secretary of the IEC). Before the first patient is enrolled in the study, all ethical and legal requirements must be met.

The IEC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised. The Investigator must keep a record of all communication with the IEC and, if applicable, between a coordinating Investigator and the IEC. This statement also applies to any communication between the Investigator (or coordinating Investigator, if applicable) and regulatory authorities.

All documents handed over to patients or their legal representative prior to use must first be reviewed and approved by sponsor, and upon approval by sponsor submitted to and reviewed and approved by, the competent IEC. This includes but is not limited to the informed consent form, patient information sheet, assent form, advertisements, training materials, etc.

12.9 ONGOING INFORMATION FOR INDEPENDENT ETHICS COMMITTEE

If required by legislation or the IEC, the investigator must submit to the IEC:

- Information on SAEs or SUSARs as per local applicable rules and timelines;
- Periodic reports on the progress of the study;
• Deviations from the protocol or anything that may involve added risk to subjects.

12.10 CLOSURE OF THE STUDY
Sponsor reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (e.g., IRB/IEC, regulatory authorities).
In addition, the Investigator or sponsor has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:
• Significant non-compliance with contractual enrolment timelines and targets
• Serious or continued GCP non-compliance
• Inaccurate, incomplete or delayed data collection
• Failure to adhere to the study protocol
• Failure to provide requested follow-up information for data queries

12.11 LIABILITY AND INSURANCE
Sponsor is responsible for obtaining insurance to set up and the conduct of the study in all participating countries and for ensuring that each sites are adequately covered. From time of entry into study (date of given consent), compulsory insurance coverage (so called subject’s insurance) will be provided for each subjects involved in the study.
Liability and insurance provisions for this study are provided in the investigator contract.

12.12 FINANCIAL DISCLOSURE
Investigators are required to provide financial disclosure information to allow sponsor to submit complete and accurate certification or disclosure statements in accordance with applicable national and local regulations. In addition, investigators must provide sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

12.13 DISCLOSURE OF PROTOCOL AND PUBLICATION POLICY
Information about this trial will be posted following the principles of the International Committee of Medical Journal Editors (ICMJE), the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) Industry Position Paper and applicable national or regional regulations and laws. The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to sponsor prior to submission. This allows sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.
Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will support publication of multicentre trials only in their entirety and not as individual centre data. In this case, a coordinating investigator will be designated by mutual agreement prior to the start of the trial.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements. Any formal publication of the study in which contribution of sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate sponsor personnel.

So-called ‘ghost writing’ is not permitted. All contributors who do not meet the criteria for authorship should be listed in an acknowledgments section. Examples of those who might be acknowledged include a person who provided purely technical help, writing assistance, or a department chairperson who provided only general support.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of sponsor, except where agreed otherwise.

13  MONITORING AND AUDITING

All aspects of the study will be monitored by sponsor or its representative for this study (sponsor authorised representative), for compliance with applicable government regulations with respect to current GCP (ICH Topic E6) and standard operating procedures. Direct access to the on-site study documentation and medical records must be ensured.

13.1  STUDY MONITORING AND SOURCE DATA VERIFICATION

Following training trial staff will be given access to the EDC system. Access to the EDC system is restricted to trial staff participating in the trial and the extent of access will depend on the participants’ user role in the trial. eCRF Completion Guidelines will be provided to the sites.

Data recorded in the eCRFs will be accessible to trial staff through internet connection.

The investigator or staff authorized by the investigator should enter subject data into electronic eCRFs in a timely manner. A separate eCRF will be used for each subject enrolled. The eCRFs must be maintained in an up-to-date condition at all times by the investigator or designee. The completed eCRFs will be signed by the investigator, or co-investigator(s) authorized by the investigator. This signature information (including date of signature) will be kept in the audit trail and is unalterable. Only medically qualified (co)investigators can sign data on clinical assessments/safety.

Any corrections made by the investigator, or authorized site staff, to the eCRF after original entry will be documented in the audit trail. Changes to data already approved, requires the re-signature of investigator or authorized staff. The audit trail will identify the person making the change and the date, time and reason for the change.
After data entry systematic data validation will be performed and any data discrepancies will be presented electronically to the site staff through the EDC system. Queries for discrepant data may be generated automatically by the software upon entry or generated manually by authorized persons such as the monitor or the trial data manager(s). All queries, whether generated by the system or by trial staff, will be in electronic format. The trial monitor will check the eCRFs for accuracy and completion and perform source data verification (SDV). The trial monitor will document electronically SDV of all sections of eCRFs used. The systematic data validation will provide a clean and consistent database prior to the statistical analysis. Data will be processed in accordance with the general terms and conditions of any national legislation. Source data verification (SDV) is a key function in assuring the sponsor that clinical trial information is recorded and handled in a way that allows its accurate reporting, interpretation and verification. Monitors will perform SDV during the conduct of the trial, to confirm the accuracy and completeness of eCRFs, and consistency of CRF entries, source documents and other trial related records against each other. To enable SDV at the trial site, it is essential to establish and agree with the investigator what constitutes source data/documents for the trial data to be collected. The location of source data will be defined in a Location of Source Data Form prior to initiation of the trial. If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. National competent authorities will be notified with the appropriate documentation. Regular monitoring visits by representatives of the sponsor will be made during the study. Monitoring will begin with an initiation visit prior to study commencement to clarify all aspects of the protocol and documentation. The purpose of later visits during the implementation period will be to evaluate study progress and adherence to the protocol. The visit intervals and detailed monitoring activities will be defined in Monitoring Guidelines. During these monitoring visits the monitor must have full access to data and documents as she/he will check CRFs for completeness, clarity and consistency with the information in subject files (source data checking). In all cases, it is the responsibility of the monitor to maintain subject confidentiality. For archiving purposes each investigator will be supplied with a copy of the eCRFs, for all subjects enrolled at the site, via an electronic medium at completion of the trial. Audit trail information will be included. The investigational sites will maintain all trial documentation, and take measure to prevent accidental or premature destruction of these documents. The Investigator, or a designated member of the Investigators’ staff, must be available during monitoring visits, audits and inspections to review data, resolve queries and allow direct access to subjects’ records (e.g. medical/hospital records, office charts, hospital charts, and study related charts) for source data and other type of verification. The Investigator must ensure timely and accurate completion of CRFs and queries.
As part of the responsibilities commensurate with participating in the study, the investigator agrees to maintain and have available for monitoring, adequate case records (accurate source documents and CRFs) for the patients treated under this protocol. In addition, the investigator agrees to maintain all administrative documents (e.g. IEC correspondence, investigational product and supplies shipment manifests, monitoring logs, or correspondence with sponsor and with any of its representative for this study).

13.2 ON-SITE AUDITS

Investigators and institutions involved in the study will permit trial-related monitoring, audits, IEC review, and domestic or foreign regulatory inspection(s) by providing direct access to source documents, CRFs, and all other study documentation.

The Investigator should promptly notify sponsor of any inspections scheduled by any regulatory authorities and promptly forward to sponsor copies of any audit reports received.

To enable evaluations and/or audits from national CA or sponsor the investigator agrees to keep records of all study documentation, including between others the identity of all participating subjects, all original signed Informed Consent Forms, a copy of all eCRFs, and detailed records of drug disposition. These should be kept in an Investigator’s File that should be provided by the sponsor and kept regularly updated by the investigator.

The eCRFs will be available for inspection by authorized representatives from sponsor, e.g. co-monitoring or audit by the sponsor, from National Competent Authority and/or EC.

13.3 SERIOUS GCP BREACHES

The sponsor or its delegates will notify in writing competent authorities and Ethics committees of any serious breach of -

- the conditions and principles of GCP in connection with that trial; or
- the protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

A “serious breach” is a breach which is likely to effect to a significant degree

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial”.

If the Sponsor or delegates obtains clear and unequivocal evidence that a serious breach has occurred, Sponsor will notify to CA and EC first, within 7 days, and investigate and take action simultaneously or after notification. In this case, the Sponsor will not wait to obtain all of the details of the breach prior to notification. In other cases, some degree of investigation and assessment may be required by the Sponsor prior to notification, in order to confirm that a serious breach has actually occurred.
Therefore, should an Investigator become aware of a possible serious GCP breach, e.g. a protocol violation, or non-reporting of critical safety information that has the potential of jeopardising patients’ safety, sponsor must be notified within 24 hours.

Sponsor will also informs the relevant Chief Investigator and Principal Investigators of the breach notification. Communication in this regard facilitates the implementation of corrective and preventative actions. Sponsor must take appropriate corrective and preventative actions in response to the serious breach, and to document these actions in follow-up reports made in writing to CAs and ECs. Sponsor will make available a clear process to identify and notify the sponsor of serious breaches. (Formal SOP and form to be faxed to sponsors or delegate)

14 DOCUMENTATION AND USE OF STUDY FINDINGS

14.1 DOCUMENTATION OF STUDY RESULTS

An electronic CRF is used in this study and a specific electronic CRF will correspond to each subject. All required information must be entered on the CRFs. If an item is not available or is not applicable, this fact should be indicated and no blank spaces must be left. The data collected on the CRF will be entered into the study database. If the investigator authorises other personnel to enter data into the CRF, the names, positions, signatures, and initials of these persons must be supplied to sponsor or their authorised representative before these individuals start completing CRF information. The CRF pages must be reviewed and signed by the Investigator named in the study protocol or by a designated sub-investigator. Sponsor will ensure that the CRF copy left with the Investigator (print-outs and/or CD-ROM) has never been under the direct or indirect control of sponsor.

14.2 USE OF COMPUTERISED SYSTEMS AT THE CLINICAL TRIAL CENTRE

The patient's right to protection against invasion of privacy will be in compliance with ICH and other local regulations (whichever is more stringent). Before entering the study each patient will receive a unique number (alphanumerical code) and all data will be linked to this code and not to any data or information that could reveal the identity of the patient. Original data content such as medical charts, will be reviewed only by dedicated staff (study monitor) and none of the information regarding patient identity will be recorded, tracked processed or exported from the clinical site. Sponsor requires the Investigator to permit trial monitors and when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws (any copies of patients’ records must be duly anonymised to protect patients’ confidentiality). Should direct access to medical records require a waiver or authorisation separate from the patient’s statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.
Data collected will be processed and analysed in aggregate manner and the alphanumeric code will be the only reference that will be used to allow identification of all the data reported for each subject in the respect of ICH 5.5.5. Individual data will be also kept in a database called an electronic case report form (e-CRF). The e-CRF will be developed in compliance with the protection of individuals with regard to personal data processing and data transfer. Data Management processes that will be followed during the study have been validated to ensure the compliance of the system both with the user requirements and the prevailing regulations. All means will be implemented to ensure the security, authenticity, integrity, and confidentiality of the data recorded in accordance with EU Directive 2002/58/EC and national requirements.

System functionalities are consistent with the 21 CFR Part 11 and GCP Requirements. Data will be secured by both physical and electronic means against damage. Regular back-ups of all relevant data should be done. Integrity and accuracy of backup data and the ability to restore the data should be checked during validation and monitored periodically. A secured audit trail with highly regulated access will be available to users and internal auditors and authorities’ inspection. The system is designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data and a list of the individuals who are authorized to make data changes will be defined according FDA Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance ICH, 1996 (ICH 5.5.3). The System will support backup and restore processes that preserve all system records, audit trails, data entry and processing in accordance with ICH 5.5.3. Technology implemented ensures that electronic signature is used properly. Suitable archiving systems will be in place to safeguard the data integrity.
14 REFERENCES


Evans NP, Misyakb SA, Robertson JL, Bassaganya-Rierab J, Grangea RW. 2009. Immune mediated mechanisms potentially regulate the disease time course of Duchenne muscular dystrophy and provide targets for therapeutic intervention. PMR.


ICH. 2003. Stability testing of new Drug substance and Products - Q1A (R2).

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APPENDIX 1: WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION
It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.
The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.
In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.
Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.
Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES
1. Biomedical research involving human subjects must conform to generally accept scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be commented and guided to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.
II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

13. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.

14. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

15. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

16. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

17. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

18. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

19. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

20. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

21. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

22. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.