Official Title: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of ACE-083 in Patients with Facioscapulohumeral Muscular Dystrophy

NCT Number: NCT02927080

Protocol A083-02

A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of ACE-083 in Patients with Facioscapulohumeral Muscular Dystrophy

SPONSOR: Acceleron Pharma Inc.
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ORIGINAL PROTOCOL DATE: 24 June 2016
AMENDMENT 01 DATE: 31 August 2016
AMENDMENT 02 DATE: 21 November 2017
AMENDMENT 03 DATE: 08 August 2018
AMENDMENT 04 DATE: 09 January 2019

Confidentiality Statement
This confidential information in this document is provided to you as an investigator or consultant for review by you, your staff, and the applicable Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from Acceleron Pharma Inc.
Signature Page

Acceleron Pharma Approval

Signature: ________________________________ Date: ________________________

Name (print): ________________________________

Investigator Agreement: I have read the protocol and agree to conduct the study as outlined in the protocol. The study will be conducted in accordance to current United States Food and Drug Administration (FDA) regulations, International Council of Harmonization (ICH) Guidelines, Good Clinical Practices (GCP), the Declaration of Helsinki, and local ethical and legal requirements.

Signature: ________________________________ Date: ________________________

Name (print): ________________________________

Institution Name and Address:

________________________________________

________________________________________

________________________________________
### PROCEDURES IN CASE OF EMERGENCY

#### Table 1: Emergency Contact Information

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<thead>
<tr>
<th>Role in Study</th>
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<td>Medical Monitor</td>
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<tr>
<td>Pharmacovigilance</td>
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<td>Pharmacovigilance</td>
<td>Medpace Clinical Safety</td>
<td>Medpace SAE Hotline-USA&lt;br&gt;Tel: 866-336-0930 or 800-730-5779 ext. 2999&lt;br&gt;Fax: 866-336-5320&lt;br&gt;Email: <a href="mailto:medpace-safetynotification@medpace.com">medpace-safetynotification@medpace.com</a></td>
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<td>[Redacted]</td>
</tr>
</tbody>
</table>
2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

1. TITLE PAGE ............................................................................................................. 1
2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES .............. 4

LIST OF TABLES .......................................................................................................... 8
3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS ......................... 9
4. PROTOCOL SYNOPSIS ....................................................................................... 11
5. INTRODUCTION .................................................................................................... 21
   5.1. Background ..................................................................................................... 21
   5.2. Study Rationale ............................................................................................ 22
6. OBJECTIVES AND ENDPOINTS ........................................................................ 23
7. STUDY DESIGN .................................................................................................... 25
   7.1. Overview of Study Design ........................................................................... 25
   7.2. Justification for Dose Level ........................................................................ 26
   7.3. Benefit/Risk Assessment ............................................................................. 26
8. STUDY POPULATION .......................................................................................... 27
   8.1. Inclusion Criteria .......................................................................................... 27
   8.2. Exclusion Criteria ........................................................................................ 28
   8.3. Screen Failures ............................................................................................. 29
9. DISCONTINUATION/WITHDRAWAL CRITERIA ................................................. 30
   9.1. Discontinuation of Study Treatment ............................................................. 30
   9.2. Withdrawal from the Study ......................................................................... 30
   9.3. Lost to Follow Up ......................................................................................... 31
10. TREATMENT OF PATIENTS ............................................................................ 32
   10.1. Treatments Administered .......................................................................... 32
   10.1.1. Individual Dose Modification Rules ....................................................... 33
   10.2. Safety Review Team (SRT) ....................................................................... 33
   10.3. Concomitant Medications ......................................................................... 34
   10.4. Treatment Compliance .............................................................................. 35
   10.5. Randomization and Blinding ..................................................................... 35
11. STUDY DRUG MATERIALS AND MANAGEMENT .......................................... 36
   11.1. Study Drug .................................................................................................. 36
11.2. Study Drug Packaging and Labeling .......................................................... 36
11.3. Study Drug Storage ................................................................................. 36
11.4. Study Drug Preparation .......................................................................... 36
11.5. Study Drug Accountability ...................................................................... 36
11.6. Study Drug Handling and Disposal .......................................................... 36
12. STUDY PROCEDURES .............................................................................. 37
12.1. Written Informed Consent ....................................................................... 37
12.2. Study Assessments .................................................................................. 37
12.3. Safety Assessments ................................................................................ 37
12.4. Efficacy Assessments .............................................................................. 37
12.5. Pharmacokinetic and Pharmacodynamic Assessments ............................. 37
13. SAFETY ....................................................................................................... 38
13.1. Definition of Adverse Events ................................................................. 38
13.1.1. Adverse Event ..................................................................................... 38
13.1.1.1. Unexpected Adverse Events ............................................................ 38
13.1.1.2. Events Not to Be Considered as Adverse Events .............................. 38
13.1.1.3. Serious Adverse Event .................................................................... 38
13.1.1.4. Events Not to Be Considered as Serious Adverse Events ............... 39
13.1.1.5. Suspected Unexpected Serious Adverse Reactions ........................ 39
13.2. Severity .................................................................................................... 39
13.3. Relationship to Study Drug ..................................................................... 39
13.4. Recording Adverse Events ..................................................................... 40
13.4.1. Documentation of Serious Adverse Events ......................................... 40
13.5. Reporting Adverse Events ...................................................................... 41
13.6. Pregnancy ................................................................................................. 41
13.7. Reporting Serious Adverse Events .......................................................... 41
13.7.1. Safety Reporting to Health Authorities, Independent Ethics Committees, Institutional Review Boards, and Investigators ...................................................... 42
14. STATISTICS .................................................................................................. 43
14.1. Analysis Populations .............................................................................. 43
14.2. Statistical Analysis Considerations .......................................................... 43
14.2.1. Patient Demographics and Disposition .............................................. 43
14.2.2. Drug Exposure ..................................................................................... 43
### APPENDIX 1. SCHEDULE OF EVENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>14.2.3. Efficacy Data</td>
<td>43</td>
</tr>
<tr>
<td>14.2.3.1. Part 1</td>
<td>43</td>
</tr>
<tr>
<td>14.2.3.2. Part 2</td>
<td>44</td>
</tr>
<tr>
<td>14.2.3.3. Exploratory</td>
<td>45</td>
</tr>
<tr>
<td>14.2.3.4. Pooled Analyses</td>
<td>45</td>
</tr>
<tr>
<td>14.2.4. Safety Data</td>
<td>45</td>
</tr>
<tr>
<td>14.2.5. Pharmacokinetic Data</td>
<td>45</td>
</tr>
<tr>
<td>14.2.6. Anti-drug Antibody Data</td>
<td>46</td>
</tr>
<tr>
<td>14.3. Determination of Sample Size</td>
<td>46</td>
</tr>
<tr>
<td>14.4. Interim Analysis</td>
<td>46</td>
</tr>
<tr>
<td>14.5. Deviation from Original Analysis Plan</td>
<td>46</td>
</tr>
<tr>
<td>15. ETHICS</td>
<td>47</td>
</tr>
<tr>
<td>15.1. Institutional Review Board</td>
<td>47</td>
</tr>
<tr>
<td>15.2. Ethical Conduct of the Study</td>
<td>47</td>
</tr>
<tr>
<td>15.3. Patient Information and Consent</td>
<td>47</td>
</tr>
<tr>
<td>15.4. Patient Data Protection</td>
<td>47</td>
</tr>
<tr>
<td>16. SOURCE DOCUMENTATION AND INVESTIGATOR FILES</td>
<td>48</td>
</tr>
<tr>
<td>16.1. Study Monitoring</td>
<td>48</td>
</tr>
<tr>
<td>16.2. Audits and Inspections</td>
<td>48</td>
</tr>
<tr>
<td>17. QUALITY CONTROL AND QUALITY ASSURANCE</td>
<td>49</td>
</tr>
<tr>
<td>17.1. Data Quality Control and Quality Assurance</td>
<td>49</td>
</tr>
<tr>
<td>17.1.1. Investigator Responsibility</td>
<td>49</td>
</tr>
<tr>
<td>17.1.2. Protocol Modifications</td>
<td>49</td>
</tr>
<tr>
<td>18. CONFIDENTIALITY</td>
<td>50</td>
</tr>
<tr>
<td>19. PUBLICATION POLICY</td>
<td>51</td>
</tr>
<tr>
<td>20. PROTOCOL AMENDMENTS</td>
<td>52</td>
</tr>
<tr>
<td>21. DATA HANDLING AND RECORDKEEPING</td>
<td>53</td>
</tr>
<tr>
<td>21.1. Case Report Form Completion</td>
<td>53</td>
</tr>
<tr>
<td>21.2. Retention of Records</td>
<td>53</td>
</tr>
<tr>
<td>22. REFERENCES</td>
<td>54</td>
</tr>
<tr>
<td>23. APPENDICES</td>
<td>55</td>
</tr>
</tbody>
</table>

**APPENDIX 2. REFERENCES**
LIST OF TABLES

Table 1: Emergency Contact Information ........................................................................3
Table 2: Abbreviations and Specialist Terms ..................................................................................9
Table 3: Objectives and Endpoints .........................................................................................23
Table 4: Cohort Schedule for Study A083-02 ........................................................................33
Table 5: Schedule of Events for Part 1: Dose Escalation, Open-Label ................................57
Table 6: Schedule of Events for Part 2: Randomized, Double-Blind, Placebo-Controlled with Open-Label Extension .........................................................59
Table 7: Clinical Safety Laboratory Assessments .........................................................................62
3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Table 2: Abbreviations and Specialist Terms

<table>
<thead>
<tr>
<th>Abbreviation or Specialist Term</th>
<th>Explanation</th>
</tr>
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<tbody>
<tr>
<td>ADA</td>
<td>Anti-drug antibody</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>AST</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BB</td>
<td>Biceps brachii</td>
</tr>
<tr>
<td>CK</td>
<td>Creatine kinase</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>CTX</td>
<td>C-terminal collagen crosslinks</td>
</tr>
<tr>
<td>DLT</td>
<td>Dose limiting toxicity</td>
</tr>
<tr>
<td>DUX4</td>
<td>Double homeobox protein 4</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
</tr>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FSHD</td>
<td>Facioscapulohumeral muscular dystrophy</td>
</tr>
<tr>
<td>FSHD-HI</td>
<td>Facioscapulohumeral muscular dystrophy-health index</td>
</tr>
<tr>
<td>FST</td>
<td>Follistatin</td>
</tr>
<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>GDF8</td>
<td>Growth and differentiation factor 8</td>
</tr>
<tr>
<td>IB</td>
<td>Investigator’s brochure</td>
</tr>
<tr>
<td>ICF</td>
<td>Informed consent form</td>
</tr>
<tr>
<td>ICH</td>
<td>International Council for Harmonisation</td>
</tr>
<tr>
<td>IEC</td>
<td>Independent ethics committee</td>
</tr>
<tr>
<td>IgG2</td>
<td>Immunoglobulin G2</td>
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<tr>
<td>IM</td>
<td>Intramuscular</td>
</tr>
<tr>
<td>IP</td>
<td>Investigational product</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional review board</td>
</tr>
<tr>
<td>MMT</td>
<td>Manual muscle testing</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>MTD</td>
<td>Maximum tolerated dose</td>
</tr>
<tr>
<td>Abbreviation or Specialist Term</td>
<td>Explanation</td>
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<tr>
<td>--------------------------------</td>
<td>-------------</td>
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<tr>
<td>NCI-CTCAE</td>
<td>National Cancer Institute-Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamic</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetic</td>
</tr>
<tr>
<td>PUL</td>
<td>Performance of the upper limb</td>
</tr>
<tr>
<td>QMT</td>
<td>Quantitative muscle testing</td>
</tr>
<tr>
<td>RF</td>
<td>Rectus femoris</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SRT</td>
<td>Safety review team</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected unexpected serious adverse reaction</td>
</tr>
<tr>
<td>TA</td>
<td>Tibialis anterior</td>
</tr>
<tr>
<td>TGF-β</td>
<td>Transforming growth factor beta</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit of normal</td>
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</table>
4. PROTOCOL SYNOPSIS

Name of Sponsor/Company: Acceleron Pharma Inc., 128 Sidney Street, Cambridge, MA 02139

Name of Investigational Product: ACE-083

Name of Active Ingredient: ACE-083 is a recombinant fusion protein consisting of a modified form of human follistatin linked to a human IgG2 Fc domain.

Title of Study: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of ACE-083 in Patients with Facioscapulohumeral Muscular Dystrophy

Study Centers: Approximately 30 centers

Phase of Development: 2

Objectives

Part 1
Primary:
• To evaluate the safety and tolerability of ACE-083 in patients with facioscapulohumeral muscular dystrophy (FSHD)

Secondary:
• To determine the recommended dose level(s) of ACE-083 for Part 2
• To evaluate change in muscle volume and intramuscular fat fraction of the injected muscle
• To evaluate change in strength of the injected muscle
• To estimate the systemic exposure of ACE-083 when administered as a local muscle injection

Exploratory:
• To evaluate changes in motor function related to the injected muscle
• To evaluate changes in patient-reported measures of FSHD-health index (FSHD-HI) total score and subscale scores

Part 2
Primary:
• To determine whether treatment with ACE-083 increases total muscle volume of the injected muscle in patients with FSHD

Secondary:
• To determine whether treatment with ACE-083 decreases intramuscular fat fraction of the injected muscle
• To determine whether treatment with ACE-083 increases strength of the injected muscle
• To determine whether treatment with ACE-083 improves motor function (e.g., six minute walk test distance, performance of upper limb [PUL] mid-level/elbow dimension assessment) related to the injected muscle
Clinical Study Protocol
Study A083-02
Revision: 04

- To evaluate changes in patient-reported measures of FSHD-HI total score and subscale scores
- To evaluate the safety and tolerability of ACE-083
- To estimate the systemic exposure of ACE-083 when administered as a local muscle injection

Exploratory (Part 2, open-label):
- To assess the effect of treatment with ACE-083 on motor function as measured by the 100-meter timed test (tibialis anterior groups) or PUL high level/shoulder dimension assessment (biceps brachii groups)

Methodology
This is a multicenter, Phase 2 study to evaluate the safety, tolerability, pharmacodynamics (PD), efficacy, and pharmacokinetics (PK) of ACE-083 in patients with FSHD, to be conducted in two parts. Part 1 is open-label, dose-escalation (3 months) and Part 2 is randomized, double-blind, placebo-controlled (6 months) followed by an open-label extension (6 months). Patients who have signed the informed consent form (ICF) and meet the eligibility criteria will be enrolled into the study.

Part 1 (dose escalation, open-label)
Part 1 will consist of up to 6 cohorts of patients and will evaluate multiple ascending dose levels of ACE-083 in either the tibialis anterior (TA) or biceps brachii (BB) muscle. Patients in each cohort will be enrolled in a 1-month screening period before beginning treatment.

Cohorts 1a and 1b will be treated in parallel. The dose level in Cohort 1a will be 150 mg (3 mL) administered by multiple injections unilaterally into the TA muscle, once every 3 weeks for up to 5 doses. Patients in Cohort 1b will be similarly treated in the BB muscle. The estimated tissue exposure of ACE-083 (mg/g muscle) is expected to be similar for the TA and the BB, as the two muscles are relatively similar in size.

For Cohorts 2a and 2b, the decision to enroll patients and the dose levels that will be administered will be based upon Safety Review Team (SRT) review of safety and, if necessary, imaging data collected in prior cohorts. The planned dose level for Cohorts 2a and 2b is 200 mg, with a maximum possible dose level of 250 mg, to be selected following SRT review of data from prior cohorts.

For Cohorts 3a and 3b, the decision to enroll patients, dose level (maximum 250 mg), muscle tested (TA and/or BB), and unilateral or bilateral dosing will be based upon SRT review of safety and imaging data collected in prior cohorts.

The SRT will meet to review data for each cohort when at least 4 patients within a cohort have completed their Day 43 visit (SRT meetings for “a” and “b” cohorts can occur separately or together, depending on recruitment). The SRT may recommend one or more of the following: treatment of the remaining patients at the current dose level; escalation to a higher dose level for the next cohort; an intermediate (lower) dose level; or no treatment of additional patients or cohorts. Recommendations made by the SRT may be relevant to both the TA and BB or specific to one or the other muscle, as safety findings and dose escalation may be specific to each muscle.
**Part 2 (randomized, double-blind, placebo-controlled, with open-label extension)**

Prior to the initiation of Part 2, a review of safety and efficacy data from Part 1 will be conducted to determine whether cohorts for one or both muscles will be pursued in Part 2, as well as the recommended dose level for each muscle. A total of up to 56 new patients (28 patients per muscle) may be enrolled and randomized (1:1) to receive either ACE-083 (n=14/muscle) or placebo (n=14/muscle) bilaterally to either the TA or BB muscles (but not both). Patients will receive blinded study drug once every three weeks for approximately 6 months (9 doses).

Patients who complete the double-blind treatment period will immediately roll over to open-label treatment of ACE-083, receiving the same dose of active drug, bilaterally in either the TA or BB muscle, once every three weeks for approximately 6 months (8 doses). In Part 2, the SRT will periodically review blinded safety data for each muscle treated.

**Number of Patients (planned)**

Up to 36 patients will be enrolled in the dose escalation phase of the study (Part 1) and up to 56 patients (14 active, 14 placebo per muscle) will be enrolled in Part 2, for a total of up to approximately 92 patients.

**Diagnosis and Main Criteria for Eligibility**

**Inclusion Criteria:**

1. Age ≥ 18 years
2. Genetically-confirmed FSHD1 or FSHD2 (or a first-degree relative with genetically confirmed FSHD1 or FSHD2) and clinical findings meeting FSHD criteria
3. **Part 1 TA cohorts:**
   a. 6-minute walk distance (6MWD) ≥ 150 meters (without a brace)
   b. Left and/or right ankle dorsiflexion Medical Research Council (MRC) manual muscle testing (MMT) grade 3 to 4+, inclusive (Appendix 3)
      
      Note: Contralateral side may be MRC MMT grade 3 to 5

   **Part 1 BB cohorts:**
   a. Left and/or right elbow flexion MRC MMT grade 3 to 4+, inclusive (Appendix 3)
      
      Note: Contralateral side may be any MRC MMT grade

4. **Part 2 TA cohorts:**
   a. 6MWD ≥ 150 and ≤ 500 meters (without a brace); a maximum of 20% of enrolled patients with 6MWD ≥ 450 meters will be included
   b. Left and right ankle dorsiflexion MRC MMT grade 3 to 4+, inclusive (Appendix 3)

5. **Part 2 BB cohorts:**
   a. Left and right elbow flexion MRC MMT grade 3 to 4+, inclusive (Appendix 3)

4. Females of childbearing potential (defined as sexually mature women who have not undergone hysterectomy or bilateral oophorectomy, or are not naturally postmenopausal ≥ 24 consecutive months) must have negative urine pregnancy test prior to enrollment and use highly effective birth control methods (abstinence, oral contraceptives, barrier method with spermicide, or surgical sterilization) during study participation and for 8 weeks following the last dose of ACE-083. Hormonal birth control use must be stable for at least
14 days prior to Day 1. Males must agree to use a condom during any sexual contact with females of childbearing potential while participating in the study and for 8 weeks following the last dose of ACE-083, even if he has undergone a successful vasectomy. Patients must be counseled concerning measures to be used to prevent pregnancy prior to the first dose of ACE-083.

5. Ability to adhere to the study visit schedule/procedures, and to understand and comply with protocol requirements

6. Signed written informed consent

Exclusion Criteria:

1. Current active malignancy (e.g., remission less than 5 years duration), with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or ≤ 2 squamous cell carcinomas of the skin

2. Symptomatic cardiopulmonary disease, significant functional impairment, or other co-morbidities that in the opinion of the investigator would limit a patient’s ability to complete strength and/or functional assessments on study

3. Renal impairment (serum creatinine ≥ 2 times the upper limit of normal [ULN])

4. Aspartate transaminase (AST) and/or alanine transaminase (ALT) ≥ 3 times ULN

5. Increased risk of bleeding (i.e., due to hemophilia, platelet disorders, or use of any anticoagulation/platelet modifying therapies up to 2 weeks prior to Study Day 1; low dose aspirin [≤ 100 mg daily] is permitted)

6. Major surgery within 4 weeks prior to Study Day 1

7. Chronic systemic corticosteroids (≥ 2 weeks) within 4 weeks before Study Day 1 and for duration of study; intra-articular/topical/inhaled therapeutic or physiologic doses of corticosteroids are permitted

8. Androgens or growth hormone within 6 months before Study Day 1 and for duration of study; topical physiologic androgen replacement is permitted

9. Any change in medications potentially affecting muscle strength or function within 4 weeks of Study Day 1 and for duration of study (e.g., creatine, CoQ10, systemic beta-adrenergic agonists)

10. Previous exposure to any investigational agent potentially affecting muscle volume, strength, or function within 5 half-lives of last dose or 4 weeks of Study Day 1 if half-life is unknown, or any prior exposure to ACE-083

11. Significant change in physical activity or exercise (e.g., significant increase or decrease in intensity or frequency) within 8 weeks before Study Day 1 or inability to maintain the baseline level of physical activity throughout the study

12. Any condition that would prevent MRI scanning or compromise the ability to obtain a clear and interpretable scan of the TA or BB muscles, as applicable (e.g., pacemaker, knee/hip replacement, or metallic implants)

13. Known active substance abuse, including alcohol

14. History of sensitivity to protein pharmaceuticals

15. Female that is lactating/breast-feeding
Investigational Product, Dosage, and Mode of Administration

ACE-083 drug product is provided as a lyophilized powder contained in stoppered and sealed glass vials. Each single-use vial will be reconstituted with sterile water and contains 1.2 mL of ACE-083 solution for injection after reconstitution. ACE-083 drug product solution for injection contains ACE-083 at a nominal concentration of 50 mg/mL.

Using electromyography (EMG) or ultrasound guidance, each dose of study drug will be administered into the non-tendinous portion of the TA or BB up to 5 equal-volume injections per muscle. The use of EMG or ultrasound guidance will ensure that viable muscle is present at the injection site. If the degree of atrophy or fibro-fatty infiltration poses administration challenges, injections of ACE-083 should be distributed at least 2 cm apart into viable muscle. Injection site locations as well as measures to avoid adjacent nerves and blood vessels and prevent intravascular injection are outlined in the Investigational Product (IP) Handling Guide.

For unilateral dosing (part 1 only), if disease involvement in the lower leg or upper arm is asymmetric, the side that is weakest should be injected provided the MRC criterion is met. For bilateral dosing in Part 1, if only one side is weak (i.e., contralateral side is MRC grade 5), it is acceptable to enroll the patient and to inject only the weak side. If a patient meets inclusion criteria for both the TA and BB, the investigator will choose one target muscle based on the patient’s clinical presentation as well as cohort availability and ability to complete assessments for muscle volume (MRI), strength, and function.

In Cohorts 1 and 2 of Part 1, each dose will be administered unilaterally into the same targeted muscle, once every 3 weeks for up to 5 doses. For optional Cohort 3, bilateral dosing may be explored (to be determined by SRT), with a maximum absolute dose level of 250 mg/muscle administered bilaterally every 3 weeks for 5 doses.

For Part 2, ACE-083 or placebo (normal saline) will be administered every 3 weeks for approximately 6 months (9 doses). Patients who complete the double-blind treatment period will immediately roll over to open-label treatment of ACE-083, receiving the same dose of active drug, bilaterally in either the TA or BB muscle, once every three weeks for approximately 6 months (8 doses).

The planned dose scheme for Part 1 is below.

### Part 1: N=Up to 36 (3-month, dose-escalation, non-randomized, open-label)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Muscle</th>
<th>Dose Levela</th>
<th>ACE-083 n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Tibialis anterior</td>
<td>150 mg</td>
<td>6</td>
</tr>
<tr>
<td>2a</td>
<td>Tibialis anterior</td>
<td>200 mgb</td>
<td>6</td>
</tr>
<tr>
<td>3a</td>
<td>Tibialis anterior</td>
<td>TBDb</td>
<td>6</td>
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<th>Cohort</th>
<th>Muscle</th>
<th>Dose Levela</th>
<th>ACE-083 n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>Biceps brachii</td>
<td>150 mg</td>
<td>6</td>
</tr>
<tr>
<td>2b</td>
<td>Biceps brachii</td>
<td>200 mgb</td>
<td>6</td>
</tr>
<tr>
<td>3b</td>
<td>Biceps brachii</td>
<td>TBDb</td>
<td>6</td>
</tr>
</tbody>
</table>

*a Injection into muscle once every three weeks  
bDose levels for Cohorts 2 and 3 to be determined by SRT, not to exceed 250 mg per muscle
The planned dose scheme for Part 2 is below.

**Part 2:** N=Up to 56\(^a\) (6-month, randomized, double-blind, placebo-controlled, with 6-month open-label extension)

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Dose Level(^b)</th>
<th>ACE-083 (n)</th>
<th>Placebo (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tibialis anterior</td>
<td>TBD(^c)</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>TBD(^c)</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

\(^a\) N=14 active, 14 placebo per muscle.

\(^b\) Injection into muscle once every three weeks

\(^c\) Based on review of Part 1, not to exceed 250 mg per muscle

**Individual Dose Modification Rules**

For an adverse event (AE, including injection site reaction) of Grade 3 or higher, regardless of relationship to study drug, treatment will be paused and the patient will be monitored weekly. Dosing may resume upon resolution of the AE to ≤ Grade 1 or baseline, at the discretion of the investigator. Dose level should be reduced by one level (i.e., from 240 to 200 mg or from 200 to 150 mg) for events related to study drug for the remainder of the study; treatment will be discontinued if event occurred at 150 mg dose.

**Duration of Study**

Study duration for a patient in Part 1 will be approximately 6 months, including a 1-month screening period, a 3-month treatment period, and a 2-month follow-up period after the last dose. Study duration for a patient in Part 2 will be approximately 15 months, including a 1-month screening period, a 12-month treatment period (6-month double-blind, placebo-controlled and a 6-month open-label extension), and a 2-month follow-up period after the last dose.

If a patient has a positive anti-drug antibody (ADA) result at the last visit, the patient will be asked to return for additional ADA testing approximately every three months, until a negative result is obtained or the result is considered to be stabilized.

**Reference Therapy, Dosage, and Mode of Administration**

The placebo (control agent) to be used in Part 2 of this study will be sterile normal saline (0.9% sodium chloride for injection). Sterile normal saline will be supplied by the investigational site’s pharmacist. The manufacturer’s directions for saline storage and handling are to be followed, as are standard clinical practices for ensuring sterility. Saline-filled syringes will be prepared by unblinded study personnel and provided to blinded study personnel for administration.
Safety Assessment:

Dose-Limiting Toxicity (DLT) Definition:

- A serious adverse event (SAE), possibly or probably related to study drug
  OR
- An adverse event (AE), injection site reaction, laboratory parameter abnormality, or vital sign abnormality, possibly or probably related to study drug, and either grade ≥ 3 (National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE], Version 4.03) or grade ≥ 2 and considered clinically significant.

Part 1 Dose Escalation Stopping Rules (under SRT review):

Dosing at current levels will continue unless the following condition occurs:

- ≥ 2 DLTs of the same character in a cohort

Safety Review Team (SRT):

An SRT, comprised at minimum of a principal investigator, medical monitor, and an independent neuromuscular specialist, will review all collected safety data when at least 4 patients in a cohort have completed their Day 43 visit.

The SRT will review safety data including but not limited to AEs, laboratory results (including hematology and chemistry), urinalysis results, and vital signs data to assess for DLTs and overall safety of each dose level within each muscle. The SRT may request collection of additional data from currently enrolled patients. Based on review of safety data, the SRT will make one or more of the following recommendations:

- Continue enrollment in current cohorts
- Open next cohort and treat
- Discontinue one or more cohorts
- Begin enrollment into Part 2
- Discontinue the study

SRT recommendations for dose escalation in Part 1 will be based in part upon the dose escalation stopping rules for each muscle. If a stopping rule is met, a lower intermediate dose may be recommended or the previous dose level will be considered the maximally tolerated dose (MTD). The SRT may also decide to cease enrollment in the presence of AEs that do not meet dose stopping rules if the nature of these AEs is deemed a significant risk to patients in a given cohort. In addition, the SRT will recommend a dose level for each muscle in Part 2. In Part 2, the SRT will periodically review blinded safety data for each muscle treated. Further details on the role of the SRT during Part 2 are included in the SRT Guidelines.

Assessments for Evaluation:

Safety: AEs, injection site reactions, concomitant medications, clinical laboratory tests (including hematology, chemistry, and ADA), urinalysis, vital signs, and physical examination findings.

Pharmacokinetics: ACE-083 serum concentrations

Pharmacodynamics: selected laboratory biomarkers (e.g., total testosterone, estradiol, serum C-terminal collagen crosslinks [CTX])
**Efficacy:**

**Muscle volume:** Muscle volume and intramuscular fat fraction in the TA and BB by MRI

**Muscle strength:** Muscle strength (maximum voluntary isometric contraction) of ankle dorsiflexion and elbow flexion measured by quantitative muscle testing (by handheld dynamometer [Part 1 and Part 2] and at selected sites by fixed system [Part 1])

**Motor function tests:** TA muscle function by 10-meter walk/run, 100-meter timed test (Part 2, open-label), 4-stair climb, 6-minute walk test, and gait analysis; BB muscle function by performance of the upper limb (PUL) testing (Appendix 4) and by upper extremity-specific FSHD-HI subscale scores

**Patient-reported disease burden and health-related quality of life:** Patient-reported measures of quality of life and self-assessments of disease burden by the FSHD-HI total score and subscale scores

**Statistical Methods:**

**Sample Size Calculation:**

**Part 1**

There is no formal sample size calculation for Part 1. Six patients in each cohort will provide sufficient data to evaluate safety and a preliminary assessment of changes in muscle volume and muscle strength.

**Part 2**

The sample size calculation for Part 2 is based upon the percent change from baseline in total muscle volume of the injected TA muscle 3 weeks after the last dose. A 10% difference between ACE-083-treated and placebo groups in the percent change in total muscle volume from baseline is considered to be clinically meaningful. The standard deviation (SD) is assumed to be approximately 9% for each group, based on preliminary MRI data for the ACE-083-treated side from the initial TA cohort in Part 1. Similar assumptions apply for treatment of the BB muscle.

Assuming a 2-sided type 1 error rate of 0.10, a 10% difference in percent change from baseline between the ACE-083-treated and placebo groups in total muscle volume, a standard deviation of 9% for each group, and a 1:1 randomization, 83% power is achieved with a total sample size of n=24 for the TA muscle (12 active, 12 placebo), based on a standard t-test.

In addition, this sample size also provides 83% power to detect a 10% difference in 6MWD, based on a similar estimated SD of 9% and a 2-sided type 1 error rate of 0.1.

In order to account for dropouts (up to 15%), 28 patients will be randomized to study treatment for each muscle (14 active, 14 placebo) to ensure that at least 12 patients per treatment group complete the double-blind treatment period.

**Analysis Populations:**

**Full Analysis Set:** Part 1: All patients enrolled in the study and have received at least one dose of study drug. Part 2: All patients randomized in the study

**Safety Population:** All patients enrolled/randomized in the study who have received at least one dose of study drug (including placebo)
Per Protocol Set: All patients enrolled/randomized in the study, who have received at least one dose of study drug (including placebo) with no major protocol violations and at least one post-baseline efficacy evaluation

Pharmacokinetics Population: All patients who have received at least one dose of study drug and have sufficient PK samples collected and assayed for PK analysis

Statistical Analysis:
Complete details regarding the statistical analyses outlined below will be presented in a separate statistical analysis plan. For statistical analyses involving safety data, these will be done on the safety population. For statistical analyses involving pharmacokinetic data, these will be done on the pharmacokinetics population. For statistical analyses involving efficacy and/or pharmacodynamics data, these will be done using the full analysis set and per protocol set populations.

Part 1: Safety, pharmacodynamic and efficacy data will be summarized by cohort. For each efficacy parameter, the absolute and percent change from baseline in the injected TA or BB and, with the exception of motor function tests and FSHD-HI total score and subscale score data, the raw and percent change from baseline of the treated, untreated, and treated minus untreated TA or BB muscle will be presented over time for patients receiving unilateral dosing of ACE-083.
For efficacy measurements that are collected multiple times during the 1-month screening period, changes observed during this time will serve as the control for each patient. They will be summarized together with post-baseline data.

Part 2: The primary efficacy parameter will be the percent change in total muscle volume from baseline of the injected TA or BB 3 weeks after the last dose of the double-blind treatment period. A repeated measures analysis of covariance model will be used to compare the two treatment groups (ACE-083 and placebo) using a 2-sided 0.10 significance level. If the 3-week post last dose data from the double-blind treatment visit are missing, the last observation will be carried forward. Additional techniques for handling missing data will also be evaluated as sensitivity analyses to the last observation carried forward approach.
Other strength and functional measurements will be tested similarly. Estimates of the effect of ACE-083 and corresponding 90% confidence intervals will be produced.
Where applicable, pooling of patient data may be done within and across Part 1 and Part 2 the details of which will be described in the statistical analysis plan. Pooling by the estimated local dose of ACE-083 in the injected muscle (i.e., mg ACE-083/g muscle) may also be performed.
AEs will be coded using the Medical Dictionary for Regulatory Activities. Incidence of treatment-emergent AEs will be presented by system organ class and preferred term. AE incidence rates will be described by cohort and by muscle with and without regard to causality.
The frequency of occurrence of overall toxicity, categorized by toxicity grades (NCI-CTCAE, Version 4.03) will be summarized. Change from baseline in clinical laboratory parameters and vital signs will be summarized across time. Shift tables will be presented for selected laboratory parameters, and vital signs. Physical examination results will be presented in listings.
Pharmacodynamic data will be listed and summarized by cohort for each scheduled time.
Listings of individual patient serum ACE-083 concentrations, actual blood sampling times, and PK parameters including graphs of concentration versus time will be prepared by dose level. PK
parameters of ACE-083 will be determined using the standard non-compartmental method. Descriptive statistics of PK parameters will be summarized by cohort.

The results of ADA testing for ACE-083 versus time as well as results following further characterization of positive ADA samples will also be presented. Exploratory analysis will be performed on the potential effect of ADA on ACE-083 PK exposure if ADA tests are determined to be positive.
5. **INTRODUCTION**

5.1. **Background**

ACE-083 is a recombinant fusion protein consisting of a modified form of human follistatin (FST) linked to a human IgG2 Fc domain. Follistatin is a member of the transforming growth factor (TGF)-β superfamily, a large family of structurally related cytokine-like proteins and cell surface receptors that play pivotal roles in the development, differentiation, and maturation of virtually all cells and tissues. Follistatin has been shown to be a potent activin antagonist through its role as a natural ligand trap, functioning as a key regulator of activin activity in body tissues. Growth and differentiation factor 8 (GDF8), also known as myostatin, is a powerful negative regulator of skeletal muscle development and growth. Inhibition of the modulating effects of both activin and myostatin on skeletal muscle growth has been identified as a promising therapeutic approach for degenerative diseases of skeletal muscle. Unlike myostatin, in which the expression and site of action is primarily restricted to skeletal muscle, activin is produced in many different tissues and mediates a wide range of biologic processes in animals and humans, throughout all stages of development. The challenge for therapeutic intervention in muscle diseases, therefore, has been in the selective inhibition of activin/myostatin activity only in the target tissue (i.e., skeletal muscle) in order to prevent or minimize undesirable off-target effects due to broad systemic inhibition of activin. ACE-083 has been engineered and developed as a locally-active ligand trap of activin and myostatin in addition to other ligands. The properties of ACE-083 are such that the drug remains primarily within the muscle(s) injected to increase mass and strength of the particular muscle(s).

As described in the ACE-083 Investigator’s Brochure (IB), a number of nonclinical pharmacology studies have been conducted with ACE-083 to define the ligand-binding properties of the molecule and assess its anabolic effects on skeletal muscle in normal animals and in a mouse model of muscle disease. Preclinical studies in normal mice and rats have demonstrated increased muscle mass as a result of increased fiber hypertrophy and not hyperplasia. This ACE-083-induced muscle hypertrophy has also been shown to translate to functional improvement in muscle strength in normal mice. ACE-083 has also been evaluated in a well-established mouse model of human Duchenne muscular dystrophy as representative of a degenerative muscle disorder. ACE-083 treatment in these mice resulted in significant increases in the mass of the injected muscle. These studies provide evidence that local inhibition of activin/myostatin by ACE-083 can increase muscle mass even in animals with a degenerative skeletal muscle disease.

In addition, Study A083-01, a phase 1, double-blind, placebo-controlled, dose-ranging study designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of local muscle injections of ACE-083 in healthy postmenopausal women has been completed. Forty-two subjects have received ACE-083 at dose levels of 50 mg to 200 mg administered as single or multiple injections into either the right rectus femoris or right tibialis anterior muscle. ACE-083 was generally safe and well tolerated in this study with no serious adverse events or grade ≥ 3 events reported. A significant dose-dependent change in volume of the injected muscle was been seen in the treated versus placebo group.
5.2. Study Rationale

The initial proposed indication for ACE-083 is facioscapulohumeral muscular dystrophy (FSHD), which is the third most common muscular dystrophy and has an autosomal dominant pattern of inheritance in most patients compared to a less common sporadic form which affects approximately 10-30% of patients.\(^6\) FSHD has a prevalence of 1:15,000-1:20,000.\(^6\) FSHD is characterized by complex genetic mechanisms relating to the double homeobox protein 4 gene (DUX4). DUX4 is normally repressed through epigenetic mechanisms in somatic cells and is derepressed in FSHD leading to toxic damage to skeletal muscle cells. The DUX4 gene is located in the D4Z4 microsatellite array in the 4q35 region. In FSHD1, one D4Z4 allele is contracted (1 to 10 repeat units) and has been associated with DNA hypomethylation and chromatin structural changes. FSHD2 accounts for about 5% of FSHD cases and has been characterized by hypomethylation of both normal D4Z4 alleles. Mutations in the SMCHD1 gene resulting in changes in the D4Z4 chromatin structure have been linked to FSHD2. Both types are phenotypically indistinguishable.\(^8\) Other rare atypical variants of the disease can also manifest in the setting of a genetic diagnosis.

FSHD patients typically present in their second decade of life and live a normal lifespan. The disease is clinically characterized by slowly progressive focal asymmetric areas of muscle weakness involving the facial, scapular, upper arm, lower leg, and abdominal muscles. Bicep and triceps involvement can affect upper arm flexion and extension limiting ability to lift objects and perform activities of daily living. Weakness of the tibialis anterior (TA), a commonly affected lower extremity muscle in FSHD patients, often results in impaired dorsiflexion and foot drop. Foot drop can lead to gait instability and falls requiring the use of braces, walking devices, and wheelchairs. About 20% of FSHD patients become non-ambulatory. Other clinical complications associated with FSHD may involve respiratory muscle weakness, resulting in pulmonary complications, retinovascular disease, chronic pain, and hearing loss.\(^9\) Laboratory and muscle biopsy findings are often non-specific and therefore are not required for diagnosis. Elevations in creatine kinase (CK) can be seen but are often normal in asymptomatic patients. Muscle biopsy can show variable changes in muscle fiber size (both hypertrophy and atrophy) and inflammatory cellular infiltrates.\(^10\)

The management of the disease is based on supportive care including pain management, physical therapy, walking devices or braces, and surgical procedures including those to stabilize the scapula and improve shoulder function. There is an extremely high unmet need for drug development in FSHD as there is no approved disease-modifying therapy for this unrelenting disease. Clinical trials have evaluated multiple systemic treatments including prednisone, albuterol, strength training, and a myostatin inhibitor without definitive positive results.\(^8\) Given the frequent involvement of isolated muscles such as the TA and biceps brachii (BB), the localized action of ACE-083 could provide meaningful improvements in a patient’s muscle strength, function, and quality of life.
6. OBJECTIVES AND ENDPOINTS

Table 3: Objectives and Endpoints

<table>
<thead>
<tr>
<th>Part</th>
<th>Objectives</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>To evaluate the safety and tolerability of ACE-083 in patients with FSHD</td>
<td>Presence and nature of AEs including injection site reactions and changes in clinical laboratory parameters.</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>To determine the recommended dose level(s) of ACE-083 for Part 2</td>
<td>Recommendation from SRT</td>
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<tr>
<td></td>
<td>To evaluate changes in muscle volume and intramuscular fat fraction of the injected muscle</td>
<td>Percent change from baseline in total muscle volume of the injected muscle</td>
</tr>
<tr>
<td></td>
<td>To evaluate changes in strength of the injected muscle</td>
<td>Percent and absolute change from baseline in intramuscular fat fraction of the injected muscle</td>
</tr>
<tr>
<td></td>
<td>To estimate the systemic exposure of ACE-083 when administered as a local muscle injection</td>
<td>Percent change from baseline in strength measurements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Systemic exposure by changes in serum concentrations over time</td>
</tr>
<tr>
<td><strong>Exploratory</strong></td>
<td>To evaluate changes in motor function related to the injected muscle</td>
<td>Percent change from baseline in functional assessments</td>
</tr>
<tr>
<td></td>
<td>To evaluate changes in patient-reported measures of FSHD-HI total score and subscale scores</td>
<td>Percent change from baseline in FSHD-HI total score</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Percent change from baseline in FSHD-HI subscale scores</td>
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### Part 2

<table>
<thead>
<tr>
<th>Objectives</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
</tr>
<tr>
<td>- To determine whether treatment with ACE-083 increases total muscle volume of the injected muscle in patients with FSHD</td>
<td>- Percent change from baseline in total muscle volume of the injected muscle</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
</tr>
<tr>
<td>- To determine whether treatment with ACE-083 decreases intramuscular fat fraction of the injected muscle</td>
<td>- Percent and absolute change from baseline in intramuscular fat fraction of the injected muscle</td>
</tr>
<tr>
<td>- To determine whether treatment with ACE-083 increases strength of the injected muscle</td>
<td>- Percent change from baseline in strength measurements</td>
</tr>
<tr>
<td>- To determine whether treatment with ACE-083 improves motor function related to the injected muscle</td>
<td>- Percent change from baseline in functional assessments (e.g., six minute walk test distance [tibialis anterior groups], performance of upper limb [PUL] mid-level/elbow dimension assessment [biceps brachii groups])</td>
</tr>
<tr>
<td>- To determine whether treatment with ACE-083 improves patient-reported measures of FSHD-HI total score and subscale scores</td>
<td>- Percent and absolute change from baseline in FSHD-HI total score as well as percent and absolute change in FSHD-HI subscale scores</td>
</tr>
<tr>
<td>- To evaluate safety and tolerability of ACE-083</td>
<td>- Presence and nature of AEs including injection site reactions and changes in clinical laboratory parameters</td>
</tr>
<tr>
<td>- To estimate the systemic exposure of ACE-083 when administered as a local muscle injection</td>
<td>- Systemic exposure by changes in serum concentrations over time</td>
</tr>
<tr>
<td><strong>Exploratory (Part 2, open-label)</strong></td>
<td></td>
</tr>
<tr>
<td>- To assess the effect of treatment with ACE-083 on selected motor function tests</td>
<td>- Percent change from baseline in 100-meter timed test (tibialis anterior groups) and PUL high-level/shoulder dimension assessment (biceps brachii groups)</td>
</tr>
</tbody>
</table>
7. STUDY DESIGN

7.1. Overview of Study Design

Study A083-02 is a multicenter, Phase 2 study to evaluate the safety, tolerability, pharmacodynamics (PD), efficacy, and pharmacokinetics (PK) of ACE-083 in patients with FSHD to be conducted in two parts. Part 1 is open-label, dose-escalation (3 months) and Part 2 is randomized, double-blind, placebo-controlled (6 months) with an open-label extension (6 months). Patients who have signed the informed consent form (ICF) and meet the eligibility criteria will be enrolled into the study. Up to 36 patients will be enrolled in Part 1 and up to 56 patients (14 active, 14 placebo per muscle) will be enrolled in Part 2, for a total of up to approximately 92 patients.

Study duration for a patient in Part 1 of the study will be approximately 6 months, including a 1-month screening period, a 3-month treatment period, and a 2-month follow-up period after the last dose. Study duration for a patient in Part 2 of the study will be approximately 15 months, including a 1-month screening period, a 12-month treatment period (6-month double-blind, placebo-controlled and a 6-month open-label extension), and a 2-month follow-up period after the last dose.

If a patient has a positive anti-drug antibody (ADA) result at the last visit, the patient will be asked to return for additional ADA testing approximately every three months, until a negative result is obtained or the result is considered to be stabilized.

Part 1 (dose escalation, open-label)

Part 1 will consist of up to 6 cohorts of patients and will evaluate multiple ascending dose levels of ACE-083 in either the tibialis anterior (TA) or biceps brachii (BB) muscle. Patients in each cohort will be enrolled in a 1-month screening period before beginning treatment.

Cohorts 1a and 1b will be treated in parallel. The dose level that will be administered in Cohort 1a will be 150 mg (3 mL) administered by multiple injections unilaterally into the TA muscle, once every 3 weeks for up to 5 doses. Patients in Cohort 1b will be similarly treated in the BB muscle. The estimated tissue exposure of ACE-083 (mg/g muscle) is expected to be similar for the TA and the BB, as the two muscles are relatively similar in size.

For Cohorts 2a and 2b, the decision to enroll patients and the dose levels that will be administered will be based upon Safety Review Team (SRT) review of safety and, if necessary, imaging data collected in prior cohorts. The planned dose level for Cohorts 2a and 2b is 200 mg, with a maximum possible dose level of 250 mg, to be selected following SRT review of data from prior cohorts.

For Cohorts 3a and 3b, the decision to enroll patients, dose level (maximum 250 mg), muscle tested (TA and/or BB), and unilateral or bilateral dosing will be based upon SRT review of safety and imaging data collected in prior cohorts.

The SRT will meet to review data for each cohort when at least 4 patients within a cohort have completed their Day 43 visit (SRT meetings for a and b cohorts can occur separately or together, depending on recruitment). The SRT may recommend one or more of the following: treatment of the remaining patients at the current dose level; escalation to a higher dose level for the next...
cohort; an intermediate (lower) dose level or no treatment of additional patients or cohorts. Recommendations made by the SRT may be relevant to both the TA and BB or specific to one or the other muscle, as safety findings and dose escalation may be specific to each muscle.

**Part 2 (randomized, double-blind, placebo-controlled, with open-label extension)**

Prior to the initiation of Part 2, a review of safety and efficacy data from Part 1 will be conducted to determine whether cohorts for one or both muscles will be pursued in Part 2, as well as the recommended dose level for each muscle. A total of up to 56 new patients (28 patients per muscle) may be enrolled and randomized (1:1) to receive either ACE-083 (n=14/muscle) or placebo (n=14/muscle) bilaterally to either the TA or BB muscles (but not both). Patients will receive study drug once every three weeks for approximately 6 months (9 doses).

Patients who complete the double-blind treatment period will immediately roll over to open-label treatment of ACE-083, receiving the same dose of active drug, bilaterally in either the TA or BB muscle, once every three weeks for approximately 6 months (8 doses). In Part 2, the SRT will periodically review blinded safety data for each muscle treated.

### 7.2. Justification for Dose Level

ACE-083 was administered into either the rectus femoris (RF) or TA muscle of healthy post-menopausal women in the Phase 1 Study A083-01 at absolute dose levels per muscle of up to 200 mg (RF) or 150 mg (TA) as either a single dose or repeated dose every 3 weeks. An estimated ACE-083 exposure (mg/g muscle) within the muscle was calculated for each patient using the dose administered to each patient and the size of each patient’s RF as measured at baseline by MRI. Exposures of approximately 1.2 to 1.6 mg drug/g muscle every 3 weeks for 2 doses in the RF resulted in the desired effect of an approximately 15% increase in muscle volume. These exposures were considered safe and generally well tolerated following review of safety information.

Considering the overall similarity in size for the TA and BB muscles, as well as the potential for muscle atrophy and fibro-fatty infiltration in FSHD patients, a starting dose level of 150 mg for both the TA and BB is considered appropriate and safe based on the Phase 1 clinical trial results. This starting dose level will protect patient safety and also ensure that the initial exposures achieved within the muscle have the potential to impact efficacy endpoints. All subsequent dose levels (higher or lower) will be determined/confirmed following review of study data and recommendations from the SRT. A maximum absolute dose/muscle of 250 mg following dose escalation has been chosen based on administration feasibility and volume constraints.

### 7.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, SAEs, and reasonably anticipated AEs of ACE-083 is provided in the IB.
8. STUDY POPULATION

8.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet all of the following criteria at screening:

Inclusion Criteria:

1. Age ≥ 18 years
2. Genetically-confirmed FSHD1 or FSHD2 (or a first-degree relative with genetically confirmed FSHD1 or FSHD2) and clinical findings meeting FSHD criteria
3. Part 1 TA cohorts:
   a. 6-minute walk distance ≥ 150 meters (without a brace)
   b. Left and/or right ankle dorsiflexion Medical Research Council (MRC) manual muscle testing (MMT) grade 3 to 4+, inclusive (Appendix 3)
      Note: Contralateral side may be MRC MMT grade 3 to 5

Part 1 BB cohorts:
   a. Left and/or right elbow flexion MRC MMT grade 3 to 4+, inclusive (Appendix 3)
      Note: Contralateral side may be any MRC MMT grade

Part 2 TA cohorts:
   a. 6MWD ≥ 150 and ≤ 500 meters (without a brace); a maximum of 20% of enrolled patients with 6MWD ≥ 450 meters will be included
   b. Left and right ankle dorsiflexion MRC MMT grade 3 to 4+, inclusive (Appendix 3)

Part 2 BB cohorts:
   a. Left and right elbow flexion MRC MMT grade 3 to 4+, inclusive (Appendix 3)

4. Females of childbearing potential (defined as sexually mature women who have not undergone hysterectomy or bilateral oophorectomy, or are not naturally postmenopausal ≥ 24 consecutive months) must have negative urine pregnancy test prior to enrollment and use highly effective birth control methods (abstinence, oral contraceptives, barrier method with spermicide, or surgical sterilization) during study participation and for 8 weeks following the last dose of ACE-083. Hormonal birth control use must be stable for at least 14 days prior to Day 1. Males must agree to use a condom during any sexual contact with females of childbearing potential while participating in the study and for 8 weeks following the last dose of ACE-083, even if he has undergone a successful vasectomy. Patients must be counseled concerning measures to be used to prevent pregnancy prior to the first dose of ACE-083.
5. Ability to adhere to the study visit schedule/procedures, and to understand and comply with protocol requirements

6. Signed written informed consent

8.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening:

1. Current active malignancy (e.g., remission less than 5 years duration), with the exception of fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or ≤ 2 squamous cell carcinomas of the skin

2. Symptomatic cardiopulmonary disease, significant functional impairment, or other co-morbidities that in the opinion of the investigator would limit a patient’s ability to complete strength and/or functional assessments on study

3. Renal impairment (serum creatinine ≥ 2 times the upper limit of normal [ULN])

4. Aspartate transaminase (AST) and/or alanine transaminase (ALT) ≥ 3 times ULN

5. Increased risk of bleeding (i.e., due to hemophilia, platelet disorders, or use of any anticoagulation/platelet modifying therapies up to 2 weeks prior to Study Day 1; low dose aspirin (≤ 100 mg daily) is permitted)

6. Major surgery within 4 weeks prior to Study Day 1

7. Chronic systemic corticosteroids (≥ 2 weeks) within 4 weeks before Study Day 1 and for duration of study; intra-articular/topical/inhaled therapeutic or physiologic doses of corticosteroids are permitted

8. Androgens or growth hormone within 6 months before Study Day 1 and for duration of study; topical physiologic androgen replacement is permitted

9. Any change in medications potentially affecting muscle strength or function within 4 weeks of Study Day 1 and for duration of study (e.g., creatinine, CoQ10, systemic beta-adrenergic agonists)

10. Previous exposure to any investigational agent potentially affecting muscle volume, strength, or function within 5 half-lives of last dose or 4 weeks of Study Day 1 if half-life is unknown, or any prior exposure to ACE-083

11. Significant change in physical activity or exercise (e.g., significant increase or decrease in intensity) within 8 weeks before Study Day 1 or inability to maintain the baseline level of physical activity throughout the study

12. Any condition that would prevent MRI scanning or compromise the ability to obtain a clear and interpretable scan of the TA or BB muscles, as applicable (e.g., pacemaker, knee/hip replacement, or metallic implants)

13. Known active substance abuse, including alcohol

14. History of sensitivity to protein pharmaceuticals
15. Female that is lactating/breast-feeding

8.3. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 additional times. The interval between rescreenings should be at least 4 weeks after the end of the 4-week screening period (i.e., the earliest re-consent may occur is 8 weeks after the prior consent was signed). Each time rescreening is performed; the individual must sign a new ICF and will be assigned a new identification number. If a test is repeated within the screening window, the patient does not need to sign a new ICF.
9. DISCONTINUATION/WITHDRAWAL CRITERIA

The reason for treatment discontinuation / study withdrawal must be recorded in the corresponding patient’s case report form (CRF). The investigator must notify the sponsor and medical monitor when a patient has been discontinued or withdrawn from the study.

All patients who are discontinued/withdrawn from the study prior to the end of treatment visit should complete the tests and evaluations (excluding the MRI if it has been done within 4 weeks of study withdrawal) scheduled for the end of treatment visit (Day 106/ET for Part 1, Day 358/ET for Part 2) at the time of discontinuation/withdrawal and will be asked to return to the clinic to complete the remaining follow-up visit assessment.

9.1. Discontinuation of Study Treatment

Reasons that may lead to discontinuation of study treatment include:

- Treatment completed
- Adverse event
- Patient request (withdrawal of consent)
- Death
- Lost to follow-up
- Pregnancy
- Protocol deviation
- Study terminated by sponsor

9.2. Withdrawal from the Study

Reasons that may lead to a patient’s withdrawal from the study include:

- Patient’s request
- Screen failure
- Patient’s unwillingness or inability to comply with the protocol
- Death
- Lost to follow-up
- Study terminated by sponsor
- Adverse event

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1 the sponsor may terminate study treatment or a dose level after consultation with the investigator and the SRT at any time for safety or administrative reasons. The sponsor will terminate the study if the occurrence of SAEs or other findings suggests unacceptable risk to the health of the patients.
9.3. **Lost to Follow Up**

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted after three attempts by the study site. Every attempt should be made to collect all data on discontinued patients.
10. TREATMENT OF PATIENTS

10.1. Treatments Administered

Using electromyography (EMG) or ultrasound guidance, each dose of study drug will be administered into the non-tendinous portion of the TA or BB as a series of up to 5 equal-volume injections. The use of EMG or ultrasound guidance will ensure that viable muscle is present at the injection site. If the degree of atrophy or fibro-fatty infiltration poses administration challenges, injections of ACE-083 should be distributed at least 2 cm apart into viable muscle. Injection site locations as well as measures to avoid adjacent nerves and blood vessels and prevent intravascular injection are outlined in the Investigational Product (IP) Handling Guide.

For unilateral dosing, if disease involvement in the lower leg or upper arm is asymmetric, the side that is weakest should be injected provided the MRC criterion is met. For bilateral dosing in Part 1, if only one side is weak (i.e., contralateral side is MRC grade 5), it is acceptable to enroll the patient and to inject only the weak side. If a patient meets inclusion criteria for both the TA and BB, the investigator will choose one target muscle based on the patient’s clinical presentation as well as on cohort availability and ability to complete assessments for muscle volume (MRI), strength, and function.

In Part 1, Cohorts 1 and 2, each dose will be administered unilaterally into the same targeted muscle, once every 3 weeks for up to 5 doses. For optional Cohort 3, bilateral dosing may be explored (determined by SRT), with a maximum absolute dose level of 250 mg/muscle administered bilaterally, every 3 weeks for 5 doses.

For Part 2, ACE-083 or placebo (normal saline) will be administered every 3 weeks for approximately 6 months (9 doses). Patients who complete the double-blind treatment period will immediately roll over to open-label treatment of ACE-083, receiving the same dose of active drug, bilaterally in either the TA or BB muscle, once every three weeks for approximately 6 months (8 doses).

The planned dose scheme for Part 1 and 2 is shown below.
Table 4: Cohort Schedule for Study A083-02

Part 1: N= Up to 36 (3-month, dose-escalation, non-randomized, open-label)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Muscle</th>
<th>Dose Level a</th>
<th>ACE-083 n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Tibialis anterior</td>
<td>150 mg</td>
<td>6</td>
</tr>
<tr>
<td>2a</td>
<td>Tibialis anterior</td>
<td>200 mg b</td>
<td>6</td>
</tr>
<tr>
<td>3a (optional)</td>
<td>Tibialis anterior</td>
<td>TBD b</td>
<td>6</td>
</tr>
</tbody>
</table>

Part 2: N=Up to 56a (6-month, randomized, double-blind, placebo-controlled and 6-month open-label extension)

<table>
<thead>
<tr>
<th>Muscle</th>
<th>6-month, double-blind, placebo-controlled</th>
<th>6-month open-label extension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose Level b</td>
<td>ACE-083 n</td>
</tr>
<tr>
<td>Tibialis anterior</td>
<td>TBD c</td>
<td>14</td>
</tr>
<tr>
<td>Biceps brachii</td>
<td>TBD c</td>
<td>14</td>
</tr>
</tbody>
</table>

10.1.1. Individual Dose Modification Rules

For an adverse event (AE, including injection site reactions) of Grade 3 or higher, regardless of relationship to study drug, treatment will be paused and the patient will be monitored weekly. Dosing may resume upon resolution of the AE to ≤ Grade 1 or baseline, and dose level may be reduced to the prior dose level deemed safe by SRT, at the discretion of the investigator. Dose level should be reduced by one level (i.e., from 240 to 200 mg or from 200 to 150 mg) for events related to study drug for the remainder of the study; treatment will be discontinued if event occurred at 150 mg dose. If dosing does not resume within 6 weeks of the last dose given, the patient will be discontinued from treatment.

10.2. Safety Review Team (SRT)

Dose-Limiting Toxicity (DLT) Definition:

- A serious adverse event (SAE), possibly or probably related to study drug

OR
An adverse event (AE), injection site reaction, laboratory parameter abnormality, or vital sign abnormality, possibly or probably related to study drug, and either grade $\geq 3$ (National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE], Version 4.03) or grade $\geq 2$ and considered clinically significant.

**Part 1 Dose Escalation Stopping Rules (under SRT review):**

Dosing at current levels will continue unless the following condition occurs:

- $\geq 2$ DLTs of the same character in a cohort

**Safety Review Team (SRT):**

An SRT, comprised at minimum of a principal investigator, medical monitor, and an independent neuromuscular specialist, will review all collected safety data when at least 4 patients in a cohort have completed their Day 43 visit.

The SRT will review safety data including but not limited to AEs, laboratory results (including hematology and chemistry), urinalysis results, and vital signs data to assess for DLTs and overall safety of each dose level within each muscle. The SRT may request collection of additional data from currently enrolled patients. Based on review of safety data, the SRT will make one or more of the following recommendations:

- Continue enrollment in current cohorts
- Open next cohort and treat
- Discontinue one or more cohorts
- Begin enrollment into Part 2
- Discontinue the study

SRT recommendations for dose escalation in Part 1 will be based in part upon the dose escalation stopping rules for each muscle. If a stopping rule is met, a lower intermediate dose may be recommended, or the previous dose level will be considered the maximally tolerated dose (MTD). The SRT may also decide to cease enrollment in the presence of AEs that do not meet dose stopping rules if the nature of these AEs is deemed a significant risk to patients in a given cohort. In addition, the SRT will recommend a dose level for each muscle in Part 2. In Part 2, the SRT will periodically review blinded safety data for each muscle treated. Further details on the role of the SRT during Part 2 are included in the SRT Guidelines.

**10.3. Concomitant Medications**

During screening and throughout the study, patients may take stable doses of medications for chronic conditions that are not specifically excluded by the protocol. If there is an immediate clinical need during the study to prescribe a new medication or a new dosage of an existing medication for either a new or chronic condition, concurrent therapy may be administered at the discretion of the investigator. Androgens or growth hormone (topical physiologic androgen replacement is permitted) and any change in medications potentially affecting muscle strength or function (e.g., creatinine, CoQ10, systemic beta-adrenergic agonists) are prohibited. The investigator may consult the medical monitor regarding what constitutes a stable dose or a
chronic condition. Information regarding concomitant medications will be collected beginning at study screening and will include all medications taken within 4 weeks prior to Study Day 1.

10.4. Treatment Compliance

Each dose of study drug will be administered as an injection at the clinical site by the study staff and will be documented in the study record. Monitoring for patient compliance with the treatment regimen is therefore unnecessary.

10.5. Randomization and Blinding

**Part 1:** This is an open-label, dose escalation phase that does not require randomization.

If a patient discontinues the study for reasons other than a safety issue related to ACE-083 and the patient had not completed the Day 43 visit, the patient may be replaced. The replacement patient will receive the same treatment as the patient replaced. Both the replacement and originally allocated patient numbers will be unique numbers.

**Part 2:** Patients who have signed the informed consent and meet all eligibility criteria will be stratified by baseline MRC MMT grade (3 to 4- and 4- to 4+) of the weaker side and then randomized to receive ACE-083 (at a dose level determined by Part 1) or placebo. Patients with a MRC MMT grade 4-may be stratified with either grade 3 to 3+ patients or 4 to 4+ patients depending on the computer-generated randomization scheme. These patients will only be included in the stratum assigned during randomization. The randomization scheme will be computer generated and will be prepared by a statistical group designated by the sponsor. If a patient discontinues the study for reasons other than a safety issue related to ACE-083 and the patient had not completed the Day 43 visit, the patient may be replaced. The replacement patient will receive the same treatment as the patient replaced. Both the replacement and originally allocated patient numbers will be unique numbers.

Among study personnel, only the pharmacist or his/her designee who prepares the study drug (ACE-083 or placebo), an unblinded clinical monitor designated by the sponsor, and the analytical laboratory will be unblinded to the patient treatment assignments. All other study personnel (including but not limited to investigators, study coordinators, nursing staff, and clinical monitors) and all patients will remain blinded to the study treatment assignments. The sponsor and the sponsor’s representatives will also remain blinded to the study treatment assignments.

In the event of a medical emergency for an individual patient in which knowledge of the study drug is critical to the patient’s medical management, the investigator may break the blind for that patient. However, prior to breaking the blind, every effort must be made by the investigator to first discuss the need to break the blind with the medical monitor. Further, it must be determined by the investigator that breaking the treatment blind is necessary information for the medical management of that patient. If the blind is broken prior to the end of treatment visit, the patient must be withdrawn from the study and complete the tests and evaluations scheduled for the end of treatment visit (Day 106/ET for Part 1 and Day 358/ET for Part 2) and will be asked to return to the clinic to complete the remaining follow-up visit assessments.
11. STUDY DRUG MATERIALS AND MANAGEMENT

11.1. Study Drug
Study drug is either ACE-083 or placebo. ACE-083 is a recombinant fusion protein consisting
of a modified form of human follistatin linked to a human IgG2 Fc domain. Placebo will be
sterile normal saline (0.9% sodium chloride for injection).

11.2. Study Drug Packaging and Labeling
ACE-083 drug product is provided as a lyophilized powder contained in stoppered and sealed
glass vials. Each single-use vial will be reconstituted with sterile water and contains 1.2 mL of
ACE-083 solution for injection after reconstitution. ACE-083 drug product solution for injection
contains ACE-083 at a nominal concentration of 50 mg/mL. Sterile normal saline for placebo
will be supplied by the investigational site’s pharmacist.

11.3. Study Drug Storage
ACE-083 should be stored at 2–8°C until use. The manufacturer’s directions for saline storage
are to be followed, as are standard clinical practices for ensuring sterility.

11.4. Study Drug Preparation
Please refer to the IP Handling Guideline, provided separately, for detailed study drug handling,
administration, and storage instructions. The manufacturer’s directions for saline handling are to
be followed, as are standard clinical practices for ensuring sterility.

11.5. Study Drug Accountability
Accountability for study drug is the responsibility of the investigator. Investigational clinical
supplies must be received by a designated person at the clinical site and kept in a secured
location. The clinical site must maintain accurate records demonstrating dates and amounts of
study drug received, to whom it was dispensed (patient-by-patient accounting), and accounts of
any study drug accidentally or deliberately destroyed or returned.

Unless otherwise notified, all vials of study drug, both used and unused, must be saved for drug
accountability purposes. The used vials may be discarded, per the institution’s standard practice,
after a drug accountability assessment has been completed by the clinical monitor. At the end of
the study, the sponsor will provide direction for the outcome of all unused vials. Following the
sponsor’s instructions, the investigator must either return all unused vials of study drug to the
sponsor or destroy them at the clinical site. In either case, the outcome must be documented on
the drug accountability log.

11.6. Study Drug Handling and Disposal
Please refer to the IP Handling Guideline, provided under separate cover, for detailed study drug
handling, administration, storage, and disposal instructions.
12. **STUDY PROCEDURES**

12.1. **Written Informed Consent**

Patients will be required to sign an independent ethics committee (IEC)/institutional review board (IRB)-approved ICF prior to any study-related procedures, including screening evaluations.

12.2. **Study Assessments**

For each patient, all study procedures should be conducted according to the Schedule of Events (Appendix 1) and following the study-specific recommendations included in the Study Manual.

12.3. **Safety Assessments**

Safety assessments include monitoring of adverse events (AEs), injection site reactions, concomitant medications, clinical laboratory assessments (including hematology, chemistry, and ADA), urinalysis, vital signs, and physical examination findings.

Please refer to Appendix 2 for the Clinical Laboratory Assessments that will be performed during this study.

12.4. **Efficacy Assessments**

**Muscle volume:** Muscle volume and intramuscular fat fraction in the TA and BB by MRI

**Muscle strength:** Muscle strength (maximum voluntary isometric contraction) of ankle dorsiflexion and elbow flexion measured by quantitative muscle testing (by handheld dynamometer [Part 1 and Part 2] and at selected sites by fixed system [Part 1])

**Motor function tests:** TA muscle function by 10-meter walk/run, 100-meter timed test (Part 2, open-label), 4-stair climb, 6-minute walk test, and gait analysis; BB muscle function by performance of the upper limb (PUL) testing (Appendix 4) and by upper extremity-specific FSHD-HI subscale scores

**Patient-reported disease burden and health-related quality of life:** Patient-reported measures of quality of life and self-assessments of disease burden by the FSHD-HI total score and subscale scores

12.5. **Pharmacokinetic and Pharmacodynamic Assessments**

Pharmacokinetic assessment includes ACE-083 serum concentrations. PK samples for patients taking concomitant medications may be analyzed for changes in cytochrome P450 enzymes.

Pharmacodynamic assessments include selected laboratory biomarkers (e.g., total testosterone, estradiol, serum C-terminal collagen crosslinks [CTX]).
13. SAFETY

13.1. Definition of Adverse Events

13.1.1. Adverse Event

For this protocol, an adverse event (AE) is any untoward medical occurrence in a clinical investigational study where a patient is administered a study drug (i.e., on or after the Cycle 1 Day 1 dose), which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study drug whether or not it is considered related to the study drug.

Abnormal laboratory and other abnormal investigational findings (e.g., physical exam, ECG) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are otherwise considered clinically relevant by the investigator.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In the case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

13.1.1.1. Unexpected Adverse Events

An unexpected AE is an AE that is not described in nature or severity in the IB under the Reference Safety Information.

13.1.1.2. Events Not to Be Considered as Adverse Events

Pre-existing medical conditions/signs/symptoms present before the screening period that do not worsen in severity or frequency during the study are defined as baseline medical conditions, and are not to be considered AEs.

13.1.1.3. Serious Adverse Event

An SAE is any AE (on or after the Cycle 1 Day 1 dose), occurring at any dose, regardless of causality, that:

- Results in death
- Is life-threatening: life-threatening means that the patient was at immediate risk of death from the reaction as it occurred (i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form)
- Requires inpatient hospitalization or prolongation of existing hospitalization; however, a hospitalization for an elective procedure will not be considered a SAE
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event: an important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the
patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

13.1.1.4. Events Not to Be Considered as Serious Adverse Events

Elective hospitalizations to administer or to simplify study treatment or perform procedures are not considered SAEs. Unexpected complications and/or prolongation of elective hospitalization should be recorded as AEs.

13.1.1.5. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and the investigator identifies a relationship to the investigational product or procedure. Acceleron follows procedures for the expedited reporting of SUSARs consistent with global regulations and associated guidances.

13.2. Severity

Investigators must evaluate the severity/intensity of AEs according to the CTCAE Version 4.03, preferentially using the graded scales. If the severity/intensity of a particular AE is not specifically graded, the investigator should apply the general guidelines for determination of Grade 1 through Grade 5 as listed in the CTCAE v4.03 cover page (reproduced below), using their best medical judgment:

**Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated

**Grade 2:** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g. preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.)

**Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living (e.g. bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)

**Grade 4:** Life-threatening consequences; urgent intervention indicated

**Grade 5:** Death related to AE

13.3. Relationship to Study Drug

Investigators must also assess the causal relationship of each AE to study drug. Factors for the assessment of causal relationship include, but are not limited to, temporal relationship between the AE and the administration of study drug, known side effects of study drug, medical history, concomitant therapy, course of the underlying disease and pertinent study procedures.
Probable: A causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of study drug and there is a reasonable response on withdrawal.

Possible: A causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of study drug.

Unlikely: A causal relationship is improbable and another documented cause of the AE is most plausible.

Not Related: A causal relationship can be definitively excluded and another documented cause of the AE is most plausible.

13.4. Recording Adverse Events

It is the responsibility of the investigator to document all AEs that occur during the study. Patients will be evaluated and questioned generally for AEs during the course of the study. The investigator must report in detail all adverse signs and symptoms which are either volunteered by patients or observed during or following the course of investigational product administration on the appropriate CRF page. All clearly related signs, symptoms, and abnormal diagnostic procedure results should be recorded as a single diagnosis. All untoward medical occurrences arising after signing of the ICF until a patient is dosed on Cycle 1 Day 1 are to be documented on the medical history CRF. All AEs occurring on or after the Cycle 1 Day 1 dose through the End of Study visit (Day 141 for Part 1 and Day 393 for Part 2) are to be reported and documented on the AE CRF.

All AEs spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the AE CRF. Any clinically relevant changes in laboratory assessments, or other clinical findings as described in Section 13.1, are considered AEs and must be recorded on the AE CRF. AEs are to be followed for resolution as described in Section 13.5.

It is important that each AE report include a description of the event, duration (onset and resolution dates), severity, relationship with ACE-083, any other potential causal factors, any treatment given, or other action taken (including dose delay or discontinuation of study drug) and outcome. In addition, SAEs should be identified and the appropriate seriousness criteria documented. AEs categorized as SAEs must also be documented using an SAE Report Form as described in Section 13.4.1.

Specific guidance can be found in the CRF Completion Guidelines provided by the Sponsor or designee.

13.4.1. Documentation of Serious Adverse Events

All SAEs that occur after the first study drug administration on Cycle 1 Day 1 until the End of Study visit (Day 141 for Part 1 and Day 393 for Part 2) are to be documented on the AE CRF.

For all SAEs, an SAE Report Form must be completed with as much information as possible and submitted within the time frame described in Section 13.7. When new significant information is obtained as well as when the outcome of an event is known, the investigator should record the
information on a new SAE Report Form. In all instances, the investigator should follow up with patients until the outcome of the SAE is known.

13.5. Reporting Adverse Events

As described in Section 13.4, all AEs must be recorded in the CRF up until the last follow-up visit. All patients who received at least one dose of study drug, whether they completed the treatment period or not, should complete the end of treatment procedures.

All AEs will be followed until clinical database lock (or resolution if it occurs before database lock). All SAEs will undergo active follow-up until the event(s) have returned to baseline status, have stabilized, or until the investigator and sponsor have agreed that follow-up is no longer necessary. Follow-up data for SAEs obtained after clinical database lock will be incorporated into the study drug safety database. If a patient experiences an SAE that is considered to be related to study treatment at any time after the study, it must be reported to the sponsor.

13.6. Pregnancy

Female patients who are of childbearing potential at the time of consent or who become of childbearing potential during study participation must agree to use a highly effective method of birth control for the duration of the study and for 8 weeks after the last dose of ACE-083.

Male patients and their partners must be using a highly effective method of birth control for the duration of the study and for 8 weeks after last dose of ACE-083.

All pregnancies occurring during the study and up to 8 weeks after the last dose of ACE-083 must be reported immediately to the investigator. The investigator must report all pregnancies to the sponsor within 24 hours of notification. A pregnant female participant must discontinue study drug immediately. Monitoring of the patient should continue until conclusion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the investigator should notify Medpace Clinical Safety. At the completion of the pregnancy, the investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e. postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting an SAE.

13.7. Reporting Serious Adverse Events

If an SAE occurs during the reporting period, the investigator must immediately (i.e., within a maximum 24 hours after becoming aware of the event) inform the CRO by telephone, fax, or e-mail.

All written reports should be transmitted using the study-specific SAE Report Form, which must be completed by the investigator following specific completion instructions. Names, addresses, telephone and fax numbers for SAE reporting are located on the SAE Report Form and in the completion instructions provided in the Study Manual. When an SAE (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail. Reporting procedures and timelines for follow-up information are the same as for the initially reported SAE.
Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant therapy). In all cases, the information provided in the SAE Report Form must be consistent with the data that are recorded in the corresponding sections of the CRF.

The investigator/reporter must respond to any request for follow-up information or to any question the Sponsor or designee may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor and (as applicable) to allow the Sponsor to meet regulatory timelines associated with expedited reporting obligations.

Requests for follow-up will usually be made by the responsible clinical monitor or medical monitor, or in exceptional circumstances by a pharmacovigilance representative who may contact the investigator directly to obtain clarification on a particularly critical event.

### 13.7.1. Safety Reporting to Health Authorities, Independent Ethics Committees, Institutional Review Boards, and Investigators

The sponsor will send appropriate safety notifications to health authorities in accordance with applicable laws and regulations.

The investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving his/her patients to the IEC or institutional review board (IRB) that approved the study.

In accordance with International Conference on Harmonization (ICH) GCP guidelines, the sponsor will inform the investigator of “findings that could adversely affect the safety of patients, impact the conduct of the study, or alter the IEC’s/IRB’s approval/favorable opinion to continue the study.”

The sponsor will inform the investigator of AEs that are serious, unexpected and are considered to be related to study drug (SUSARs). The investigator should place copies of these Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to investigators will be followed.

When specifically required by regulations and guidelines, the sponsor will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting by the sponsor is not clearly defined by national or site-specific regulations, the investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports and for filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Union Clinical Trials Directive 2001/20/EC, the Sponsor’s responsibilities regarding the reporting of SAEs/SUSARs will be carried out in accordance with that Directive and with the related Detailed Guidances.
14. **STATISTICS**

14.1. **Analysis Populations**

Full Analysis Set: Part 1 - All patients enrolled in the study and have received at least one dose of study drug. Part 2 - All patients randomized in the study

Safety Population: All patients enrolled/randomized in the study who have received at least one dose of study drug (including placebo)

Per Protocol Set: All patients enrolled/randomized in the study, who have received at least one dose of study drug (including placebo) with no major protocol violations and at least one post baseline efficacy evaluation

Pharmacokinetics Population: All patients who have received at least one dose of study drug and have sufficient PK samples collected and assayed for PK analysis

14.2. **Statistical Analysis Considerations**

A review of the available data from Part 1 will be conducted prior to enrolling patients into Part 2. Safety and changes in efficacy parameters will be reviewed across cohorts and muscles to determine which dose levels, dose regimens, and muscles will be explored in Part 2. Further details will be described in a separate statistical analysis plan.

14.2.1. **Patient Demographics and Disposition**

Individual patient demographic data will be listed by patient.

Descriptive statistics (N, mean, SD, median, minimum, and maximum) will be provided for continuous demographic variables (age, weight, height, and BMI) and frequency counts will be tabulated for categorical demographic variables (gender, race, ethnicity) by treatment and overall for each study part (Part 1 and Part 2). Age will be calculated based on birth date and informed consent date.

Individual patient disposition data will be listed by patient.

Frequency counts will be tabulated for disposition data and will consist of the number of patients completing the study (Yes / No) along with frequency counts of primary reason for discontinuation (provided there is at least one patient who discontinued). Summaries will be provided by treatment and overall for each study part (Part 1 and Part 2).

14.2.2. **Drug Exposure**

Individual study drug administration data will be listed by patient. Descriptive statistics of study drug exposure will be presented.

14.2.3. **Efficacy Data**

14.2.3.1. **Part 1**

MRI
MRI variables will include total muscle volume (TMV) [mm$^3$], intramuscular fat fraction (FF) [%] and other calculated volume and mass parameters.

**Muscle strength**

- (For TA muscle): Ankle dorsiflexion peak force value which is the maximum of three measurements from the hand-held dynamometer or fixed system,
- (For BB muscle): Elbow flexion peak force value which is the maximum of three measurements from the hand-held dynamometer or fixed system

For each parameter in unilateral cohorts, the raw data as well as the absolute and percent change from baseline in the treated TA or BB muscle, untreated TA or BB muscle, and the treated minus untreated TA or BB muscle will be summarized for each scheduled time point. For dose cohorts where the administration is bilateral, descriptive statistics of raw data, absolute and percent change from baseline will be provided by side treated [right and left] as well as the mean of the right and left sides for MRI and muscle strength parameters.

Baseline is defined as the last non-missing value prior to first dose of ACE-083. Theoretically, this should be the Day 1 pre-dose value. Such summaries will also be done for raw data and change from baseline for each primary efficacy parameter.

Estimates of the effect of ACE-083 on each efficacy parameter and corresponding 90% confidence intervals will be produced for the percent change data described above. For muscle strength parameters, the percent change from the screening to the baseline value will serve as the control for each cohort.

Additional analyses may be performed as appropriate.

**14.2.3.2. Part 2**

**Primary**

The primary efficacy endpoint is the percent change in total muscle volume three weeks post last dose of the double-blind treatment period from baseline, where baseline is defined as the last non-missing value prior to first dose of study drug.

The percent change in total muscle volume at each visit from baseline of the injected TA or BB will be summarized using descriptive statistics. Descriptive statistics will be provided by side treated [treated and untreated] as well as the mean of the right and left sides (if bilateral treatment). The effect of ACE-083 on the percent change in total muscle volume from baseline of the injected TA or BB three weeks post last dose of the double-blind treatment period versus placebo will be tested using a repeated analysis of covariance model using a two-sided 0.10 significance level. If such data is missing, the last observation will be carried forward. Additional techniques for handling missing data will also be evaluated as sensitivity analyses to the last observation carried forward approach.

Additional analyses may be performed as appropriate.

**Secondary**

**MRI**
MRI variables will include intramuscular fat fraction (FF) (%) and other calculated volume and mass parameters.

**Muscle strength**

Muscle strength parameters are defined similarly as that for Part 1. For each muscle strength parameter, descriptive statistics of the raw data, absolute and the percent change from baseline will be summarized for each scheduled timepoint. Baseline is defined as the last non-missing value prior to dosing. Descriptive statistics will be provided by side treated [treated and untreated] as well as the mean of the right and left sides (if bilateral treatment).

Estimates of the effect of ACE-083 versus placebo for the percent change in muscle strength from baseline along with the corresponding 90% confidence interval will be provided. A statistical model appropriate for this data will be used to generate the point estimates and 90% confidence intervals for these parameters as well as to perform a test of the effect of ACE-083 on these parameters versus placebo.

Additional analyses may be performed as appropriate.

Muscle function data will be summarized descriptively. Other analyses may be performed as appropriate.

FSHD-HI total and subscale scores will be summarized using descriptive statistics. Other analyses may be performed as appropriate.

**14.2.3.3. Exploratory**

Muscle function data and FSHD-HI total score and subscale scores assessed from Part 1 and 100-meter timed test and high-level/shoulder dimension PUL results from Part 2 open-label will be summarized descriptively. Other analyses may be performed as appropriate.

**14.2.3.4. Pooled Analyses**

Where applicable, pooling of patient data may be done within and across Part 1 and Part 2, the details of which will be described in the statistical analysis plan. Pooling by the estimated local dose of ACE-083 in the injected muscle (i.e., mg ACE-083/g muscle) may also be performed.

**14.2.4. Safety Data**

AEs will be coded using the Medical Dictionary for Regulatory Activities. Incidence of treatment-emergent AEs will be presented by system organ class SOC and preferred term. AE incidence rates will be described by cohort and by muscle with and without regard to causality. The frequency of occurrence of overall toxicity, categorized by toxicity grades (NCI-CTCAE, Version 4.03) will be summarized. Change from baseline in clinical laboratory parameters and vital signs will be summarized across time. Shift tables will be presented for selected laboratory parameters, and vital signs. Physical examination results will be presented in listings.

**14.2.5. Pharmacokinetic Data**

Listing of individual patient serum ACE-083 concentrations, actual blood sampling times, and PK parameters including graphs of concentration versus time will be prepared by dose level. PK
parameters of ACE-083 will be determined using the standard non-compartmental method. Descriptive statistics of PK parameters will be summarized by cohorts.

14.2.6. Anti-drug Antibody Data

The results of ADA testing for ACE-083 versus time will be listed and summarized. Exploratory analysis will be performed on the potential effect of ADA on ACE-083 PK exposure if ADA tests are determined to be positive.

14.3. Determination of Sample Size

There is no formal sample size calculation for Part 1. Six patients in each cohort will provide sufficient data to evaluate safety and a preliminary assessment of changes in muscle volume and muscle strength.

The sample size calculation for Part 2 is based upon the percent change from baseline in total muscle volume of the injected TA muscle 3 weeks after the last dose. A 10% difference between ACE-083-treated and placebo groups in the percent change in total muscle volume from baseline is considered to be clinically meaningful. The standard deviation (SD) is assumed to be approximately 9% for each group, based on preliminary MRI data for the ACE-083-treated side from the initial TA cohort in Part 1. Similar assumptions apply for treatment of the BB muscle.

Assuming a 2-sided type 1 error rate of 0.10, a 10% difference in percent change from baseline between ACE-083-treated and placebo groups in total muscle volume, a standard deviation of 9% for each group, and a 1:1 randomization, 83% power is achieved with a total sample size of n=24 for the TA muscle (12 active, 12 placebo), based on a standard t-test.

In addition, this sample size also provides 83% power to detect a 10% difference in 6-minute walk test distance, based on a similar estimated SD of 9% and a 2-sided type 1 error rate of 0.10.

In order to account for dropouts (up to 15%), 28 patients will be randomized to study treatment for each muscle (14 active, 14 placebo) to ensure that at least 12 patients per treatment group complete the double-blind treatment period.

14.4. Interim Analysis

For Part 1, periodic reviews of the available safety and tolerability will be done to assist dose escalation decisions.

For Part 2, no interim analyses are planned.

14.5. Deviation from Original Analysis Plan

A formal statistical analysis plan for the analysis and presentation of data from this study will be prepared before the database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.
15. **ETHICS**

15.1. **Institutional Review Board**

The investigator will submit this protocol, any protocol modifications, and the patient ICF to be used in this study to the appropriate IRB/IEC for review and approval. A letter confirming IRB/IEC approval of the protocol and ICF as well as a statement that the IRB/IEC is organized and operates according to GCP and the applicable laws and regulations, must be forwarded to the sponsor prior to the enrollment of patients into the study. A copy of the approved ICF will also be forwarded to the sponsor. Appropriate reports on the progress of the study will be made to the IEC and the sponsor by the principal investigator in accordance with applicable governmental regulations and in agreement with the policy established by the sponsor.

15.2. **Ethical Conduct of the Study**

The sponsor and the investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

15.3. **Patient Information and Consent**

Informed written consent is required from each patient prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the study center’s IEC, must follow the Protection of Human Patients regulations listed in the Code of Federal Regulations, Title 21, Part 50. The principles of informed consent in the Declaration of Helsinki should be implemented in this clinical study and should comply with local and national regulations. The consent forms must be in a language fully comprehensible to the prospective subject. Information should be given in both oral and written form whenever possible and deemed appropriate by the IEC.

The background of the proposed study and the benefits and risks of the procedures and study must be explained to the patients. It is the responsibility of the investigator to obtain consent and to provide the patient with a copy of the signed and dated ICF. Confirmation of a patient’s informed consent must also be documented in the patient’s medical record prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IEC and by the sponsor or designee. The ICF must not be altered without the prior agreement of the relevant IEC and the sponsor.

15.4. **Patient Data Protection**

Prior to any testing under this protocol, including screening tests and evaluations, patients must authorize the release and use of protected health information, as required by local law.

The patient will not be identified by name in the CRF or in any study reports. These reports will be used for research purposes only. The sponsor, its designee, and various government health agencies may inspect the records of this study. Every effort will be made to keep the patient’s personal medical data confidential.
16. SOURCE DOCUMENTATION AND INVESTIGATOR FILES

16.1. Study Monitoring

The clinical monitor will arrange to visit the clinical sites at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements, and continued adequacy of the clinical sites and their facilities. During these visits, CRFs and other data related to the study will be reviewed and any discrepancies or omissions will be resolved. The clinical monitor will be given access to study–relevant source documents (including medical records) for purposes of source data verification.

16.2. Audits and Inspections

The investigators and clinical sites will permit trial-related monitoring, audits, IEC review, and regulatory inspections as requested by FDA or other health authorities and the sponsor or designee. In addition to CRFs, the clinical site will permit direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed ICFs, etc.). During and/or after completion of the study, quality assurance officers named by the sponsor or the regulatory authorities may wish to perform on-site audits. The investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.
17. QUALITY CONTROL AND QUALITY ASSURANCE

17.1. Data Quality Control and Quality Assurance

17.1.1. Investigator Responsibility

The investigator is responsible for ensuring the study is conducted according to the protocol, Code of Federal Regulations, GCP, and applicable regulatory requirements. The investigator’s responsibilities are outlined in these documents and must include the responsibility to obtain a signed informed consent prior to patient participation in the study.

17.1.2. Protocol Modifications

The investigator should not modify the protocol without agreement from the sponsor and prior review or approval by the IEC, unless an emergency situation requires protocol modification to ensure the safety of patients. Any deviations from the protocol should be documented by the investigator or designee.
18. CONFIDENTIALITY

To maintain patient privacy, all CRFs, study drug accountability records, study reports and communications will identify the patient by the assigned patient identification number. The investigator will grant clinical monitor(s) and auditor(s) from the sponsor or designee and regulatory authorities’ access to the patient’s original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patient’s confidentiality will be maintained and will not be made publicly available. The patient’s medical information will only be released to the extent permitted by the applicable laws and regulations.

All information regarding the investigational product supplied by the sponsor to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the sponsor. It is understood that there is an obligation to provide the sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authorities, other investigators, corporate partners, or consultants as required.
19. PUBLICATION POLICY

All information concerning study drug is considered confidential and shall remain the sole property of the sponsor. The investigator(s) agrees to use this information only in conducting the study and shall not use it for any other purposes without the sponsor’s written approval. The investigator(s) agrees not to disclose the sponsor’s confidential information to anyone except to persons involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and non-use.

It is understood by the investigator(s) that the information developed from this clinical study will be used by the sponsor in connection with the development of study drug, and therefore may be disclosed as required to regulatory agencies. To allow for the use of the information derived from clinical studies, it is understood that there is an obligation to provide the sponsor with complete test results and all data developed in the study.

No publication or disclosure of study results will be permitted except as specified in a separate, written, agreement between the sponsor and the investigator(s).
20. PROTOCOL AMENDMENTS

Protocol amendments that impact patient safety, change the scope of the investigation, or affect the scientific quality of the study must be approved by the IEC and submitted to the appropriate regulatory authorities before implementation.

In the event that the protocol needs to be modified immediately to eliminate an apparent hazard to a patient, the sponsor will implement the protocol change and subsequently amend the protocol and notify the regulatory authorities and/or the IEC, as appropriate.
21. DATA HANDLING AND RECORDKEEPING

21.1. Case Report Form Completion

CRFs will be completed for each enrolled patient. It is the investigator’s responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient’s CRF. Source documentation supporting the CRF data should indicate the patient’s participation in the study and should document the dates and details of study procedures, AEs, and patient status.

Investigators will maintain copies of the CRFs at the clinical site. For patients who discontinue or terminate from the study, the CRFs will be completed as much as possible, and the reason for the discontinuation or termination clearly and concisely specified on the appropriate CRF.

21.2. Retention of Records

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product, or according to applicable regulatory requirements. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.
22. REFERENCES


23. APPENDICES
APPENDIX 1. SCHEDULE OF EVENTS
### Table 5: Schedule of Events for Part 1: Dose Escalation, Open-Label

<table>
<thead>
<tr>
<th></th>
<th>Screening Period</th>
<th>Treatment Period</th>
<th>Follow-Up Period</th>
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<tr>
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<td>Day -28</td>
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<td>Upper Arm Functional</td>
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<td>Assessments&lt;sup&gt;13&lt;/sup&gt;</td>
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<tr>
<td>FSHD-Health Index</td>
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<td>concomitant medications</td>
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<td>Monitoring of adverse</td>
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<td>events</td>
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<tr>
<td>Study drug</td>
<td></td>
<td></td>
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<tr>
<td>administration&lt;sup&gt;14&lt;/sup&gt;</td>
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</table>
1. Study procedures must be done prior to administration of study drug. Reference the Study Manual for the order of study procedures. Laboratory samples and functional/strength assessments may be collected up to 24 hours prior to administration of study drug. Time of study drug administration is the time of the first injection.

2. Patients who discontinue prior to the Day 106/ET visit should complete the Day 106/ET visit at the time of discontinuation and return for the remaining follow-up period visit. If an MRI has been completed within 4 weeks of discontinuation, it does not need to be repeated as part of the Day 106/ET visit procedures.

3. Pregnancy test for women of childbearing potential to be performed and negative result confirmed before dosing.

4. Full physical examination (skin, head, eyes, ears, nose, throat and neck, lymph nodes, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological) at screening and Day 106/ET; limited physical examination (skin, cardiovascular, respiratory, musculoskeletal, and neurological assessments) for Days 1, 22, 43, 64, 85.

5. Injection site examination including but not limited to evaluating erythema, pain, bruising, bleeding, and other signs of discomfort or skin reaction to be completed at least 30 minutes after injection.

6. Vital signs (weight, heart rate, systolic and diastolic blood pressure) must be taken prior to administration of study drug on dosing days. Height is collected only at screening.

7. Tests defined in Appendix 2, Table 7.

8. If a patient has a positive ADA result at Day 141, the patient will be asked to return to the clinical site for additional follow-up approximately every 3 months until a negative or stable result is obtained.

9. PK samples on a dosing day have a ±15 minute window for post-dose sample collection, based on time of first injection. Pre-dose samples may be collected up to 4 hours prior to dosing. Day 2 and 86 sample collection should be 24 hours post dose ±3 hours.

10. MRI assessments should be completed within 5 days prior to the scheduled dose administration. MRI assessments during the follow up period (Day 106/ET and Day 141) have a ± 5 day window.

11. Maximum voluntary isometric contraction testing (MVICT) of both TA and BB muscles will be conducted for all cohorts at screening visits and Day 141 only using a handheld dynamometer, only the muscle under study will be tested (i.e., TA or BB). Both sides will be tested for all visits (right and left).

12. TA cohort only: 10-meter walk/run, 4-stair climb, 6-minute walk test, and gait analysis; lower leg assessments will be collected for the BB cohorts at screening visits and Day 141 only.

13. BB cohort only: PUL testing (middle domain) testing; PUL testing (middle domain) will also be performed on patients in TA cohorts at screening visits and Day 141 only. Non-ambulatory patients in the BB cohort can opt out of the TA screening tests.

14. Study drug administration should occur within 21 days (± 3 days) of the previous dose.

15. All visit day windows should be considered relative to the date of the previous dose of study drug. Actual visit days may be different than planned (e.g., Day 8, Day 22) due to windows on visits and potential dosing delays.

16. Genetic testing for FSHD1/FSHD2 to be performed at screening if patient has not already had testing performed or previous results cannot be used to determine eligibility. Genetic testing for FSHD1/FSHD2 to be performed during the study if first degree relative is used for study eligibility but patient has not had testing previously performed or if patient’s genetic documentation is inadequate with respect to FSHD1 D4Z4 fragment size or repeat number.
Table 6: Schedule of Events for Part 2: Randomized, Double-Blind, Placebo-Controlled with Open-Label Extension

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<th>Planned Day(s)</th>
<th>Cycle(s)</th>
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<th>3</th>
<th>4</th>
<th>5</th>
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<th>7</th>
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<th>10, 15</th>
<th>16</th>
<th>11, 12, 13, 14, 17</th>
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<th>EOS&lt;sup&gt;18,20&lt;/sup&gt;</th>
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<td>(190, 295)&lt;sup&gt;1&lt;/sup&gt;</td>
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<tr>
<td>Anti-drug antibody</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>Serum PK&lt;sup&gt;10&lt;/sup&gt;</td>
<td>0, 2, 4, 6 h</td>
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<td>X</td>
<td>0, 2, 4, 6 h</td>
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<td>ECG (12 lead)</td>
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<td>Bilateral MRI&lt;sup&gt;11&lt;/sup&gt;</td>
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09 January 2019
Acceleron Pharma Inc.
<table>
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<tr>
<th>Cycle(s)</th>
<th>Screening</th>
<th>Double-Blind, Placebo-Controlled</th>
<th>Open-Label</th>
<th>ET†</th>
<th>EOS&lt;sup&gt;18,20&lt;/sup&gt;</th>
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<tr>
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<td>Planned Day(s)</td>
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<tr>
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<td>-28 to -21</td>
<td>-7 (±3d)</td>
<td>1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>2</td>
<td>8 (±1d)&lt;sup&gt;2&lt;/sup&gt;</td>
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<td>Strength (QMT – by handheld device)&lt;sup&gt;12&lt;/sup&gt;</td>
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<td>X</td>
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<td>Lower Leg Functional Assessments&lt;sup&gt;13&lt;/sup&gt;</td>
<td>TA &amp; BB</td>
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<td>TA</td>
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<td>BB &amp; TA</td>
<td>BB &amp; TA</td>
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<td>BB</td>
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<td>Upper Arm Functional Assessments&lt;sup&gt;14&lt;/sup&gt;</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>FSHD-Health Index</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>Monitoring of concomitant medications</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Monitoring of adverse events</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Randomization&lt;sup&gt;15&lt;/sup&gt;</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td></td>
<td>Study drug administration&lt;sup&gt;16&lt;/sup&gt;</td>
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<td>X</td>
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<td>MMT assessment (MRC)</td>
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<td>X</td>
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</tbody>
</table>

09 January 2019
Acceleron Pharma Inc. Page 60 of 64 CONFIDENTIAL
Clinical Study Protocol
Study A083-02

Revision: 04

1. Study procedures must be done prior to administration of study drug. Reference the Study Manual for the order of study procedures. Laboratory samples and functional/strength assessments may be collected up to 24 hours prior to administration of study drug. Time of study drug administration is the time of the first injection. The Day 1 visit is timed relative to the Screening Day -28 to Day -21 visit. The Day -7 visit is timed relative to the scheduled Day 1 visit.

2. All visit day windows should be considered relative to the date of the previous dose of study drug. Actual visit days may be different than planned (e.g., Day 8, Day 22) due to windows on visits and potential dosing delays.

3. Pregnancy test for women of childbearing potential to be performed and negative result confirmed before dosing.

4. Genetic testing for FSHD1/FSHD2 to be performed at screening if patient has not already had testing performed or previous results cannot be used to determine eligibility. Genetic testing for FSHD1/FSHD2 to be performed during the study if first degree relative is used for study eligibility but patient has not had testing previously performed or if patient’s genetic documentation is inadequate with respect to FSHD1 D4Z4 fragment size or repeat number.

5. Full physical examination includes skin, head, eyes, ears, nose, throat and neck, lymph nodes, cardiovascular, respiratory, gastrointestinal, musculoskeletal, and neurological.

6. Limited physical examination includes skin, cardiovascular, respiratory, musculoskeletal and neurological assessments.

7. Injection site examination including but not limited to evaluating erythema, pain, bruising, bleeding, and other signs of discomfort or skin reaction to be completed at least 30 minutes after injection.

8. Vital signs (weight, heart rate, systolic and diastolic blood pressure) must be taken prior to administration of study drug.

9. Tests defined in Appendix 2, Table 7.

10. PK samples on a dosing day have a ±15 minute window for post-dose sample collection, based on the time of the first injection. Pre-dose samples may be collected up to 4 hours prior to dosing. Day 2 and 86 sample collection should be 24 hours post dose ±3 hours.

11. MRI assessments should be completed within 5 days prior to the scheduled dose administration. MRI assessments during the follow up period (Day 358/ET and Day 393/EOS) have a ± 5 day window.

12. Maximum voluntary isometric contraction testing (MVICT) of both TA and BB muscles will be conducted for all cohorts at screening visits, Day 190 and Day 393/EOS. At all other visits, only the muscle under study will be tested (i.e., TA or BB). Both sides will be tested for all visits (right and left).

13. TA cohort only: 10-meter walk/run, 4-stair climb, 6-minute walk test, and gait analysis are performed at all visits: 100-meter timed test begins at Day 169 and continues throughout open-label visits; lower leg assessments will be collected for the BB cohorts at screening visits, Day 190 and Day 393/EOS only.

14. BB cohort only: PUL mid-level/shoulder dimension performed at all visits; additional PUL high level/shoulder dimension begins at Day 169 and continues throughout open-label visits; PUL testing will also be performed on patients in TA cohorts at screening visits (mid level), Day 190 (high and mid-level) and Day 393/EOS (high and mid-level) only.

15. Non-ambulatory patients in the BB cohort can opt out of the TA assessments.

16. Randonization should occur within 24 hours prior to Day 1 dose.

17. Study drug administration should occur within 21 days (± 3 days) of the last dose.

18. Patients who discontinue prior to the Day 358/ET visit should complete the Day 358/ET visit at the time of discontinuation and return for the remaining follow-up period visit. If an MRI has been completed within 4 weeks of discontinuation, it does not need to be repeated as part of the Day 358/ET visit procedures.

19. If a patient has a positive ADA result at Day 393/EOS, the patient will be asked to return to the clinical site for additional follow-up approximately every 3 months until a negative or stable result is obtained.

20. ECG is to be conducted ±1 hour of the 4h PK sample.

21. If subjects enroll directly into a separate extension study and will receive additional treatment with ACE-083, they do not need to complete the EOS visit. For these subjects, their final Study Visit in this protocol will be the ET visit.
APPENDIX 2. CLINICAL SAFETY LABORATORY ASSESSMENTS

Table 7: Clinical Safety Laboratory Assessments

<table>
<thead>
<tr>
<th>Type of Assessment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>Hemoglobin, hematocrit, platelet count, red blood cell count, white blood cell (WBC) count, and WBC differential</td>
</tr>
<tr>
<td>Chemistry</td>
<td>AST, ALT, lactate dehydrogenase (LDH) and isoenzymes 1-5, gamma-glutamyl transpeptidase (GGT), blood urea nitrogen (BUN), creatinine, creatine kinase (CK), myoglobin, aldolase, sodium, potassium, glucose, albumin, total bilirubin</td>
</tr>
<tr>
<td>Urine</td>
<td>Urinalysis by dipstick analysis (pH, specific gravity, protein, myoglobin, glucose, ketones, blood, leukocyte esterase, and nitrite)</td>
</tr>
</tbody>
</table>
### APPENDIX 3. MEDICAL RESEARCH COUNCIL MANUAL MUSCLE TESTING GRADING SCALE

Grading Scale for Manual Muscle Testing (MMT)\textsuperscript{11}

<table>
<thead>
<tr>
<th>MMT Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Normal strength</td>
</tr>
<tr>
<td>5-</td>
<td>Uncertain muscle weakness</td>
</tr>
<tr>
<td>4+</td>
<td>Inability to resist against maximal pressure throughout range of motion</td>
</tr>
<tr>
<td>4</td>
<td>Ability to resist against moderate pressure throughout range of motion</td>
</tr>
<tr>
<td>4-</td>
<td>Ability to resist against minimal pressure throughout range of motion</td>
</tr>
<tr>
<td>3+</td>
<td>Ability to move through full range of motion against gravity and to resist against minimal pressure through partial range of motion, then contraction breaks abruptly</td>
</tr>
<tr>
<td>3</td>
<td>Ability to move through full range of motion against gravity</td>
</tr>
<tr>
<td>3-</td>
<td>Ability to move through greater than one half range of motion against gravity</td>
</tr>
<tr>
<td>2+</td>
<td>Ability to move through less than one half range of motion against gravity</td>
</tr>
<tr>
<td>2</td>
<td>Ability to move through full range of motion with gravity eliminated</td>
</tr>
<tr>
<td>2-</td>
<td>Ability to move in any arc of motion with gravity eliminated</td>
</tr>
<tr>
<td>1</td>
<td>A flicker of movement is seen or felt in the muscle</td>
</tr>
<tr>
<td>0</td>
<td>No contraction palpable</td>
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</tbody>
</table>
APPENDIX 4. PERFORMANCE OF THE UPPER LIMB TEST

Performance of the Upper Limb\textsuperscript{12}