1. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company: Acceleron Pharma
Name of Finished Product: Not Applicable
Name of Active Ingredient: ACE-083</td><td>Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td>(For National Authority Use Only)</td></tr>
<tr><td colspan="3">Title of Study: A Phase 2 Randomized, Double-Blind, Placebo-Controlled Study of ACE-083 in Patients with Facioscapulohumeral Muscular Dystrophy</td></tr>
<tr><td colspan="3">Investigators: Dr Anthony Amato, Dr Urvi Desai, Dr Chafic Karam, Dr Samantha LoRusso, Dr Nanette Joyce, Dr Perry Shieh, Dr Jeffrey Statland, Dr Georgious Manousakis, Dr Rabi Tawil, Dr Russell Butterfield, Dr Alan Pestronk, Dr Lauren Elman, Dr Katherine Mathews, Dr Jeffrey Guptill, Dr Cynthia Bodkin, Dr Kathryn Wagner, Dr Matthew Wickland, Dr Waqar Waheed, Dr Scott Vota, Dr Craig Campbell, Dr Lawrence Korngut, Dr Angela Genge, Dr Jordi Diaz Manera, Dr Juan Vilchez Padilla, Dr Josep Gamez Carbonell</td></tr>
<tr><td colspan="3">Study site(s) and countries: Twenty-five study centers in 3 countries (Canada, Spain, and the United States) participated in the study, of which 2 centers screened but did not enroll any subjects (Site 1123 [Dr Waqar Waheed] and Site 1125 [Dr Scott Vota])</td></tr>
<tr><td colspan="3">Publications (reference): None</td></tr>
<tr><td colspan="2">Study periods (months): Part 1 ~6; Part 2 ~15
Date first subject enrolled: 22 November 2016
Date last subject completed: 09 October 2019</td><td>Phase of development: 2</td></tr>
<tr><td colspan="3">Trial registry number: NCT02927080
ClinicalTrials.gov identifier: NCT02927080
EudraCT number: 2016-003257-15</td></tr>
<tr><td colspan="3">Objectives:
<u>Part 1</u>
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 outcome (PRO) measures of FSHD-health index (FSHD-HI) total score and subscale scores</td></tr>
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Part 2

Primary

- To determine whether treatment with ACE-083 increases total muscle volume (TMV) 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 [6MWD], performance of upper limb [PUL] mid-level/elbow dimension assessment) related to the injected muscle
- To determine whether treatment with ACE-083 improves PRO measures of FSHD-HI total score and subscale scores
- To evaluate safety and tolerability of ACE-083
- To estimate the systemic exposure of ACE-083 when administered as a local muscle injection

Exploratory

- To assess the effect of treatment with ACE-083 on selected motor function tests

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

Part 1 (dose escalation, open-label)

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

Cohorts 1a and 1b were treated in parallel. The dose level in Cohort 1a was 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 were similarly treated in the BB muscle. The estimated tissue exposure of ACE-083 (mg/g muscle) was expected to be similar for the TA and the BB, as the two muscles are relatively similar in size.

For Cohorts 2a (TA) and 2b (BB), the decision to enroll patients and the dose levels that were administered were 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 was 200 mg administered unilaterally, with a dose selected following SRT review of data from prior cohorts.

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Based on the SRT review of safety and imaging data collected in prior cohorts, it was decided to utilize the optional Cohort 3, and patients received 200 mg/muscle bilaterally (Cohort 3a; TA) or 240 mg/muscle unilaterally (Cohort 3b; BB) every 3 weeks for 5 doses.

The SRT met to review data for each cohort when at least 4 patients within a cohort had completed their Day 43 visit (SRT meetings for "a" and "b" cohorts could occur separately or together, depending on recruitment). The SRT could 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 could be relevant to both the TA and BB or specific to one or the other muscle, as safety findings and dose escalation could 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 was conducted to determine whether cohorts for one or both muscles would be pursued in Part 2, as well as the recommended dose level for each muscle. Up to 56 new patients (28 patients per muscle) were enrolled and randomized (1:1) to receive either ACE-083 (n = 14 patients per muscle) or placebo (n = 14 patients per muscle) bilaterally to either the TA or BB muscles (but not both). Patients received blinded study drug once every 3 weeks for approximately 6 months (9 doses).

Patients who completed the double-blind treatment period immediately continued into open-label treatment with ACE-083, receiving the same dose of active drug, bilaterally in either the TA or BB muscle, once every 3 weeks for approximately 6 months (8 doses). In Part 2, the SRT periodically reviewed blinded safety data for each muscle treated.

Number of subjects (planned, enrolled, and analyzed): Up to 36 patients were planned in the dose escalation phase of the study (Part 1) and up to 56 patients (14 active, 14 placebo per muscle) were planned in Part 2, for a total of up to approximately 92 patients. In Part 1 of the study, 37 patients were treated and analyzed (18 TA, 19 BB). In Part 2 of the study, 58 patients (29 in each cohort) were treated and analyzed.

Diagnosis and main criteria for inclusion:

Key inclusion criteria were as follows:

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. 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

      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

      Note: Contralateral side may be any MRC MMT grade

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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

Part 2 BB cohorts:

a. Left and right elbow flexion MRC MMT grade 3 to 4+, inclusive

Key exclusion criteria were as follows:

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 and/or alanine transaminase ≥ 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] was 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 were permitted
8. Androgens or growth hormone within 6 months before Study Day 1 and for duration of study; topical physiologic androgen replacement was 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, coenzyme Q10, 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 magnetic resonance imaging (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)

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Test product, dose, and mode of administration: ACE-083 drug product was provided as a lyophilized powder contained in stoppered and sealed glass vials. Each single-use vial was reconstituted with sterile water and contained 1.2 mL of ACE-083 solution for injection after reconstitution. ACE-083 drug product solution for injection contained ACE-083 at a nominal concentration of 50 mg/mL.

Each dose of study drug was administered into the non-tendinous portion of the TA or BB up to 5 equal-volume injections per muscle using electromyography (EMG) or ultrasound guidance. The use of EMG or ultrasound guidance ensured that viable muscle was present at the injection site. If the degree of atrophy or fibro-fatty infiltration posed administration challenges, injections of ACE-083 were distributed at least 2 cm apart into viable muscle.

Duration of treatment:

Part 1: ACE-083 dosed every 3 weeks for up to 5 doses.

Part 2, double-blind: ACE-083 or placebo dosed every 3 weeks for up to 9 doses.

Part 2, open-label: ACE-083 dosed every 3 weeks for up to 8 doses.

Reference therapy, dose, and mode of administration: Placebo (control agent) used in Part 2 of the study was sterile normal saline (0.9% sodium chloride for injection).

Criteria for evaluation:

Safety: adverse events (AEs), injection site reactions, concomitant medications, clinical laboratory tests (including hematology, chemistry, and anti-drug antibodies [ADA]), urinalysis, vital signs, and physical examination findings.

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 test, 100-meter timed test (Part 2, open-label), 4-stair climb test, 6MWD, and gait analysis; BB muscle function by PUL testing.

Patient-reported disease burden and health-related quality of life: FSHD-HI total score and subscale scores.

Pharmacokinetics: ACE-083 serum concentrations.

Pharmacodynamics: Selected laboratory biomarkers (e.g., total testosterone, estradiol, and serum C-terminal collagen crosslinks).

Statistical methods:

Sample Size Calculation:

There was no formal sample size calculation for Part 1. Six patients in each cohort provided sufficient data to evaluate safety and a preliminary assessment of changes in muscle volume and muscle strength. The sample size calculation for Part 2 was based upon the percent change from baseline in TMV of the injected TA muscle 3 weeks after the last dose. A 10% difference between ACE-083-treated and placebo-treated groups in the percent change in TMV from baseline was

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considered to be clinically meaningful. The standard deviation (SD) was 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 applied 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-treated groups in TMV, 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 provided 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 were to be randomized to study drug for each muscle (14 active, 14 placebo) to ensure that at least 12 patients per treatment group completed the double-blind treatment period.

Part 1:

Safety, pharmacodynamic, and efficacy data were 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 were presented over time for patients receiving unilateral dosing of ACE-083. For efficacy measurements that were collected multiple times during the 1-month screening period, changes observed during this time served as the control for each patient. They were summarized together with post-baseline data.

Part 2:

The primary efficacy parameter was the percent change in TMV 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 was 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 were missing, the last observation was carried forward. Other strength and functional measurements were tested similarly. Estimates of the effect of ACE-083 and corresponding 90% confidence intervals were produced.

General:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (Version 19.1). Incidence of treatment-emergent AEs was presented by system organ class and preferred term. Adverse event incidence rates were described by cohort and by muscle with and without regard to causality. The frequency of occurrence of overall toxicity, categorized by toxicity grades (National Cancer Institute-Common Terminology Criteria for Adverse Event, Version 4.03), was summarized. Change from baseline in clinical laboratory parameters and vital signs were summarized across time. Shift tables were presented for selected laboratory parameters and vital signs. Physical examination results were presented in listings.

Pharmacodynamic data were listed and summarized by cohort for each scheduled time.

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

The results of ADA testing for ACE-083 versus time as well as results following further characterization of positive ADA samples were also presented.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS

Part 1:

Increases in TMV were dose-dependent, with > 15% mean increase observed at doses of 200 and 240 mg/muscle, but not at 150 mg/muscle. The increased muscle volume was mostly due to increases in the contractile muscle fraction. The results supported further investigation planned in Part 2 of the study.

Part 2:

The study met the primary endpoint for statistically significant improvement (percent change) from baseline to Day 190 in TMV in the ACE-083 group compared with the placebo group (least squares mean difference) for both the TA and BB cohorts. Statistically significant differences between ACE-083 and placebo were also observed for percent change in CCMV (increase) in both the TA and BB cohorts, and for change in percent fat fraction (decrease) in the TA cohort.

A statistically significant increase in mean elbow flexion strength in the BB cohort was observed for ACE-083 compared with placebo at Day 190. The improvement was not maintained during the open-label treatment period, however.

During the placebo-controlled period, there were no statistically significant differences in FSHD-HI total score or subscale scores for ACE-083 compared with placebo. A statistically significant difference in the FSHD-HI arm/shoulder subscale score was observed in pre-defined subgroups of mildly affected patients in the BB cohort in the placebo-controlled period. The full ACE-083 group showed a trend for further improvement in the arm/shoulder subscale score during the open-label period.

No other secondary or exploratory endpoints for functional or disease-related quality of life measures were considered positive. Changes in a positive direction were observed in both the ACE-083 and placebo groups for certain motor function tests, notably the 6MWD, suggesting a learning and/or placebo effect.

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SAFETY RESULTS

Overall, administration of local muscle injections of ACE-083 at doses ranging from 150 to 240 mg/muscle every 3 weeks was safe and well tolerated in adult patients with FSHD, including a subset of patients in Part 2 of the study who received active drug for up to 1 year. There were no deaths and no SAEs or life-threatening AEs considered related to the study drug reported during the study. Three patients were discontinued due to TEAEs, 2 of which were considered related to the study drug (severe muscle swelling and moderate paresthesia).

Part 1:

ACE-083 was generally well tolerated in patients treated for up to 3 months (5 doses) and no SAEs were reported. The most frequently reported TEAEs were injection site reactions and myalgia, and were mostly Grade 1-2 events. There was one reported Grade 3 event of muscle swelling in the 200 mg TA cohort, which was considered probably related to study drug. There were no clinically significant laboratory abnormalities on treatment.

Part 2:

ACE-083 was well tolerated in patients treated bilaterally in either the BB or TA muscles. Four SAEs were reported during the double-blind treatment period and one SAE was reported during the open-label treatment period; none of the SAEs was considered related to study drug.

In the TA cohort, injection site reactions were more common in patients treated with ACE-083 than in patients treated with placebo. In the BB cohort, myalgia and injection site swelling were more common in patients treated with ACE-083 than in patients treated with placebo. The incidence of ADA during double-blind treatment was 39% in the ACE-083 treatment group compared with 3% in the placebo treatment group.

CONCLUSION

Clinical investigation of ACE-083 in patients with FSHD was discontinued because the statistically significant increase in TMV failed to translate to statistically significant improvements in functional or disease-related quality of life secondary endpoints in the study.

Date of the Report: 17 July 2020