**Supplementary Material for:**

**Randomized Phase 2 Study of ACE-083, a Muscle-Promoting Agent, in Facioscapulohumeral Muscular Dystrophy**

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**Supplementary Table 1.** LS Mean (SEM) change in FSHD-HI total and subscale scores to day 190 (Part 2, per protocol set, double-blind period)

|                    | LS mean (SEM) | Difference (ACE-083–placebo) | 90% CI    | P value |
|--------------------|---------------|------------------------------|-----------|---------|
| **Biceps brachii** |               |                              |           |         |
| Placebo (n = 14)   | 2.3 (2.41)    | ACE-083 (n = 14)              | –2.1 (3.61)| –6.1, 5.8| 0.98    |
| Absolute change in FSHD-HI total score | 2.3 (2.41) | 2.1 (2.61) | –0.11 (3.62) | –6.1, 5.8 | 0.98 |
| Absolute change in FSHD-HI arm/shoulder score | 0.92 (3.83) | –3.8 (4.05) | –4.7 (5.60) | –13.9, 4.5 | 0.40 |
| Absolute change in FSHD-HI activity score | –1.6 (3.52) | –2.0 (3.62) | –0.35 (5.08) | –8.7, 8.0 | 0.95 |
| **Tibialis anterior** |               |                              |           |         |
| Placebo (n = 14)   | 2.5 (2.35)    | ACE-083 (n = 13)              | –2.0 (3.46)| –7.7, 3.7| 0.57    |
| Absolute change in FSHD-HI total score | 2.5 (2.35) | 0.53 (2.53) | –2.0 (3.46) | –7.7, 3.7 | 0.57 |
| Absolute change in FSHD-HI mobility/ambulation score | 0.06 (2.94) | –0.91 (3.20) | –1.0 (4.34) | –8.1, 6.2 | 0.82 |
| Absolute change in FSHD-HI activity score | 1.2 (3.45) | 3.3 (3.70) | 2.1 (5.07) | –6.2, 10.4 | 0.68 |

CI, confidence interval; FSHD-HI, facioscapulohumeral muscular dystrophy Health Index; LS, least squares; SEM, standard error of the mean.
**Supplementary Table 2.** Summary of related TEAEs* occurring in ≥10%† of participants (Parts 1 and 2, safety sets)

| Part 1 | Biceps brachii – ACE-083 | Tibialis anterior – ACE-083 |
|--------|--------------------------|---------------------------|
| n (%)  | 150 mg Uni (n = 6) | 200 mg Uni (n = 7) | 240 mg Uni (n = 6) | 150 mg Uni (n = 6) | 200 mg Uni (n = 6) | 200 mg Bi (n = 6) |
| Injection-site pain | 1 (16.7) | 2 (28.6) | 2 (33.3) | 5 (83.3) | 4 (66.7) | 3 (50.0) |
| Injection-site erythema | 2 (33.3) | 0 | 3 (50.0) | 0 | 1 (16.7) | 3 (50.0) |
| Injection-site bruising | 1 (16.7) | 3 (42.9) | 2 (33.3) | 0 | 1 (16.7) | 1 (16.7) |
| Injection-site discomfort | 5 (83.3) | 0 | 2 (33.3) | 1 (16.7) | 1 (16.7) | 3 (50.0) |
| Myalgia | 2 (33.3) | 1 (14.3) | 1 (16.7) | 1 (16.7) | 1 (16.7) | 2 (33.3) |
| Injection-site swelling | 1 (16.7) | 2 (28.6) | 2 (33.3) | 0 | 2 (33.3) | 1 (16.7) |
| Injection-site pruritus | 1 (16.7) | 0 | 1 (16.7) | 0 | 0 | 1 (16.7) |
| Injection-site warmth | 0 | 1 (14.3) | 0 | 0 | 0 | 1 (16.7) |
| Peripheral swelling | 0 | 0 | 1 (16.7) | 0 | 0 | 0 |
| Pain in extremity | 0 | 0 | 0 | 2 (33.3) | 0 | 1 (16.7) |
| Musculoskeletal stiffness | 0 | 0 | 0 | 0 | 0 | 0 |
| Joint swelling | 0 | 0 | 0 | 0 | 0 | 1 (16.7) |
| Injection-site discoloration | 0 | 0 | 2 (33.3) | 0 | 0 | 0 |
| Period                        | Double-blind | Open-label | Double-blind | Open-label |
|------------------------------|--------------|------------|--------------|------------|
| Injection-site pain          | Placebo (n = 15) | ACE-083 (n = 14) | Placebo (n = 15) | ACE-083 (n = 14) |
|                              | 4 (26.7)     | 4 (28.6)   | 4 (15.4)     | 3 (21.4)   |
| Injection-site erythema      | 3 (20.0)     | 3 (21.4)   | 7 (26.9)     | 6 (42.9)   |
| Injection-site bruising      | 5 (33.3)     | 4 (28.6)   | 6 (23.1)     | 1 (7.1)    |
| Injection-site discomfort    | 0            | 2 (14.3)   | 2 (7.7)      | 2 (14.3)   |
| Myalgia                      | 0            | 4 (28.6)   | 1 (3.8)      | 2 (14.3)   |
| Injection-site swelling      | 0            | 2 (14.3)   | 5 (19.2)     | 1 (7.1)    |
| Injection-site pruritus      | 1 (6.7)      | 2 (14.3)   | 3 (11.5)     | 5 (35.7)   |
| Injection-site warmth        | 0            | 1 (7.1)    | 2 (7.7)      | 3 (21.4)   |
| Peripheral swelling          | 0            | 2 (14.3)   | 0            | 1 (7.1)    |
| Pain in extremity            | 0            | 1 (7.1)    | 0            | 0          |
| Musculoskeletal stiffness    | 0            | 0          | 3 (11.5)     | 1 (7.1)    |
| Joint swelling               | 0            | 0          | 0            | 2 (14.3)   |
| Injection-site discoloration | 1 (6.7)      | 0          | 0            | 0          |

*Related TEAEs are TEAEs that are deemed possibly or probably related to study drug. Any events where the assessment of relationship is missing are assumed to be probably related.

†≥10% of participants and >1 participant in any treatment group in Part 1 or Part 2.

Bi, bilateral; TEAE, treatment-emergent adverse event; Uni, unilateral.
**Supplementary Table 3.** Summary of related TEAEs,* TEAEs leading to dose reduction or discontinuation, and fatal TEAEs (Parts 1 and 2, safety sets)

| Part 1 | Biceps brachii – ACE-083 | Tibialis anterior – ACE-083 |
|--------|--------------------------|---------------------------|
|        | 150 mg Uni (n = 6) | 200 mg Uni (n = 7) | 240 mg Uni (n = 6) | 150 mg Uni (n = 6) | 200 mg Uni (n = 6) | 200 mg Bi (n = 6) |
| n (%) |              |              |              |              |              |              |
| ≥1 related TEAE | 6 (100.0) | 5 (71.4) | 5 (83.3) | 5 (83.3) | 4 (66.7) | 5 (83.3) |
| ≥1 related TEAE with CTCAE grade ≥3 | 0 | 0 | 0 | 0 | 1 (16.7) | 0 |
| ≥1 related SAE | 0 | 0 | 0 | 0 | 0 | 0 |
| ≥1 TEAE leading to dose interruption | 0 | 0 | 0 | 0 | 0 | 0 |
| ≥1 TEAE leading to dose reduction | 0 | 0 | 0 | 0 | 1 (16.7) | 0 |
| ≥1 TEAE leading to drug withdrawal | 0 | 0 | 0 | 0 | 1 (16.7) | 0 |
| Fatal TEAE | 0 | 0 | 0 | 0 | 0 | 0 |

| Part 2 | Biceps brachii | Tibialis anterior |
|--------|----------------|------------------|
| Period | Double-blind | Open-label | Double-blind | Open-label |
| n (%) | Placebo (n = 15) | ACE-083 (n = 14) | Placebo (n = 15) | ACE-083 (n = 14) | ACE-083 (n = 27) |
| ≥1 related TEAE | 6 (40.0) | 10 (71.4) | 12 (46.2) | 8 (53.3) | 10 (71.4) | 12 (44.4) |
| ≥1 related TEAE with CTCAE grade ≥3 | 0 | 0 | 0 | 0 | 0 | 0 |
| ≥1 related SAE | 0 | 0 | 0 | 0 | 0 | 0 |
| ≥1 TEAE leading to dose interruption | 0 | 0 | 0 | 0 | 0 | 1 (3.7) |
| ≥1 TEAE leading to dose reduction | 0 | 0 | 0 | 0 | 1 (7.1) | 0 |
| ≥1 TEAE leading to drug withdrawal | 0 | 1 (7.1) | 0 | 0 | 0 | 1 (3.7) |
| Fatal TEAE | 0 | 0 | 0 | 0 | 0 | 0 |

*Related TEAEs are TEAEs that are deemed possibly or probably related to study drug. Any events where the assessment of relationship is missing are assumed to be probably related.

AE, adverse event; Bi, bilateral; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; TEAE, treatment-emergent adverse event; Uni, unilateral.