PNS PERIPHERAL NERVE SOCIETY
2018 PNS ANNUAL MEETING BALTIMORE MARYLAND JULY 22-25 Renaissance Baltimore Harborplace Hotel

Preliminary Phase 2 Results for ACE-083, Local Muscle Therapeutic, in Patients with CMT1 and CMTX

Florian P Thomas[1], Michael Shy[2], David Herrmann[3], Colin Quinn[4], Jeffrey Statland[5], David Walk[6], Nicholas Johnson[7], SH Subramony[8], Chafic Karam[9], Tahseen Mozaffar[10], Stephanie D'Eon[11], Barry Miller[11], Chad E Glasser[11], Matthew L Sherman[11], Kenneth M Attie[11]

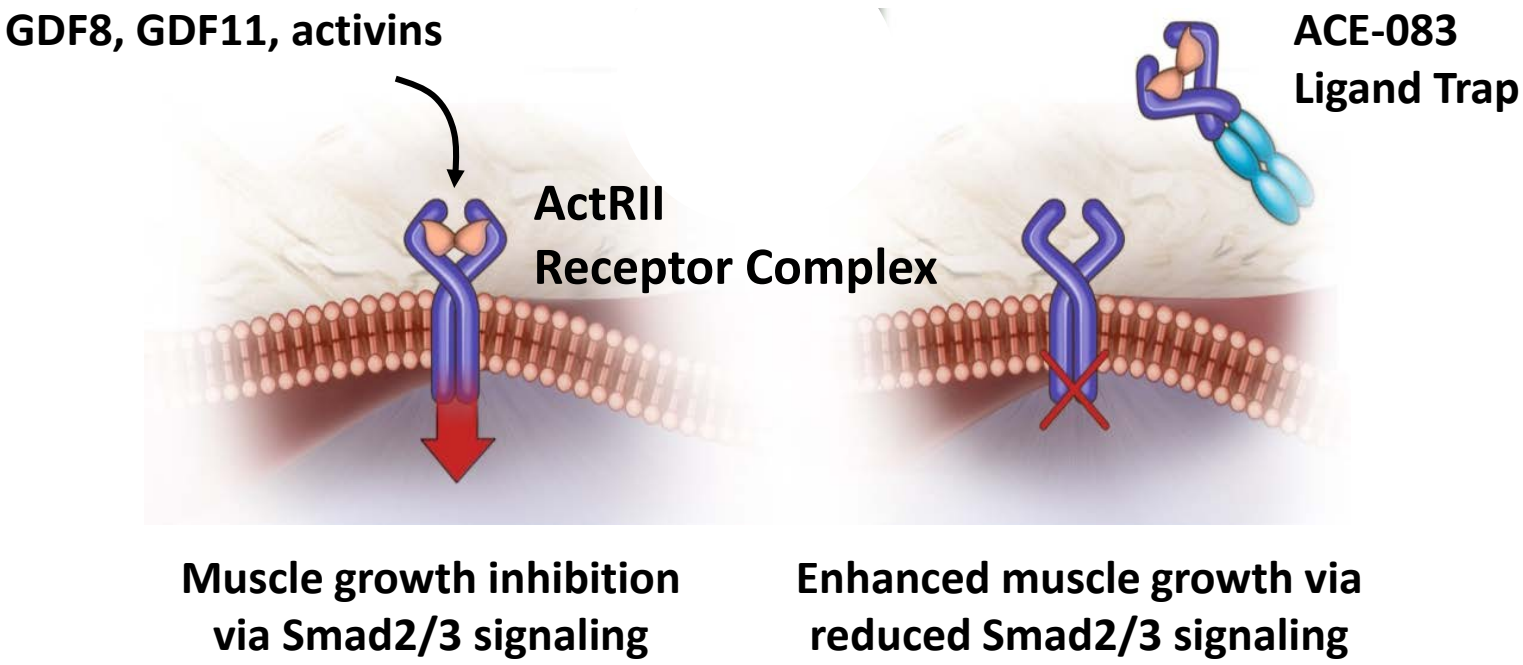
[1]Hackensack Meridian School of Medicine at Seton Hall University, [2]University of Iowa, [3]University of Rochester, [4]University of Pennsylvania, [5]University of Kansas Medical Center, [6]University of Minnesota, [7]Virginia Commonwealth University, [8]University of Florida, [9]Oregon Health & Science University, [10]University of California, [11]Acceleron Pharma

Charcot-Marie-Tooth (CMT) Disease – Introduction

- CMT is the most common inherited peripheral neuropathy with roughly 125,000 patients in the US affected
- CMT is a slowly progressive neuropathy that causes predominantly distal arm and leg weakness, motor and sensory nerve loss, and foot and ankle deformities
  - Tibialis anterior (TA) weakness is a cardinal manifestation of disease, with virtually all patients developing weak ankle dorsiflexion, often early in their disease course
  - Weakness of the TA muscle causes foot drop, impairs ambulation, and increases risk of falls
- CMT has substantial unmet medical need with no drug therapies currently available
  - Orthotics and various forms of bracing can be helpful, but compromise gait mechanics and may lead to muscle atrophy and discomfort

ACE-083 – A Locally-Acting Muscle Therapeutic

- ACE-083 is a locally-acting protein therapeutic in the TGF-β superfamily consisting of a modified form of human follistatin that binds GDF8 (myostatin) *plus* other negative regulators of skeletal muscle
- Designed to be locally injected in affected muscles to increase muscle mass and strength
- Increased muscle mass demonstrated in healthy volunteers[1] and patients with FSH muscular dystrophy[2]



[1] *Glasser CE, et al. Muscle Nerve. 2018; 57:921-926*
[2] *Statland J, et al. American Academy of Neurology, 2018*

Phase 2 Study of ACE-083 in CMT (Ongoing)

Treatment:

- ACE-083 or placebo injected bilaterally into TA muscle every 3 weeks

Part 1 – *3 mos open-label ACE-083*

Cohort 1
ACE-083 150 mg
N=6

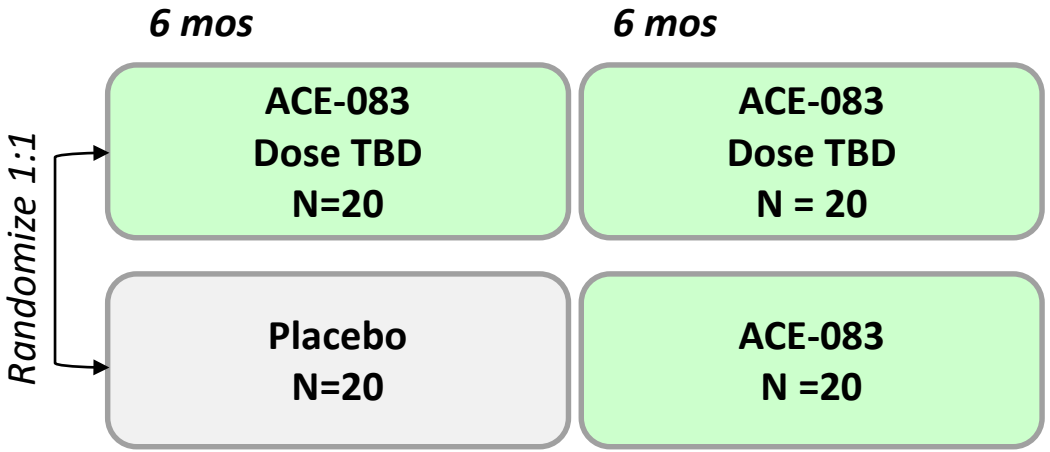
→ **Cohort 2**
ACE-083 200 mg
N=6

→ **Cohort 3**
ACE-083 240 mg
N=6

Key Assessments

- Safety & tolerability
- Identify optimal dose
- Muscle volume
- Fat fraction

Part 2 – *6 mos placebo-controlled → 6 mos open-label*



Assessments

- Muscle volume
- Fat fraction
- Strength/Function
- Quality of life
- Safety

PNS 2018

ACE-083 in CMT Study

Key Eligibility Criteria for Part 1:

- Age ≥ 18 years
- Genetically-confirmed CMT1 or CMTX, or, genetically-confirmed first-degree relative and clinical signs/symptoms of CMT1 or CMTX
- 6-minute walk distance ≥ 150 meters
- Left and right ankle dorsiflexion weakness (MRC grade 4- to 4+)
- No severe deformity or (surgical) fixation of ankle

ACE-083 CMT Study Efficacy/Pharmacodynamic Endpoints

	Assessment	Outcome Measure
Muscle Size/Quality	• Muscle and fat volumes by MRI	• Percent change in total muscle and contractile muscle volume • Absolute change in fat fraction
Muscle Strength	• Hand-held dynamometry	• Percent change in dorsiflexion strength
Muscle Function	• 6-minute walk test • 10m walk/run • Berg Balance Scale • Gait analysis	• Change/percent change in functional parameters
Investigator-/ Patient-Reported Outcomes	• CMT Examination Score (Version 2)[1] • CMT-Health Index (QoL)[2]	• Change in CMTES2 score/sub-scores • Change in CMT-HI score/sub-scores

[1] *Murphy SM, et al. Journal of the Peripheral Nervous System 2011 16:191–198*
[2] *http://rochester.technologypublisher.com/technology/22384*

ACE-083 CMT Study – Baseline Characteristics

Part 1

- Median duration of symptoms was 23 years. Median fat fraction was 30%.

	Cohort 1 150 mg N=6	Cohort 2 200 mg N=6	Cohort 3 240 mg N=6	Overall N=18
Age, yr	35 (23-62)	39 (18-61)	52 (31-58)	48 (18-62)
Gender, n (%)				
Male	3 (50%)	3 (50%)	2 (33%)	8 (44%)
Female	3 (50%)	3 (50%)	4 (67%)	10 (56%)
Duration of symptoms, yr	31 (14-61)	30 (6-51)	12 (2-25)	23 (2-61)
CMT subtype, n (%)				
CMT1	5 (83%)	5 (83%)	5 (83%)	15 (83%)
CMTX	1 (17%)	1 (17%)	1 (17%)	3 (17%)
Total muscle mass, g	66 (38-87)	70 (40-85)	92 (73-141)	78 (38-141)
Fat fraction, %	29 (10-45)	31 (15-37)	27 (9-44)	30 (9-45)
6MWD, m	418 (236-588)	381 (324-501)	459 (265-620)	411 (236-620)

Median (range), unless otherwise indicated

Preliminary data as of 05July2018

Safety Results

ACE-083 CMT Study – Safety Summary

Part 1

- ACE-083 was generally well tolerated in subjects treated for up to 3 months (5 doses)
  - Most adverse events were mild or moderate (grades 1-2)
  - Most common adverse events were injection site reactions, muscle spasms, and myalgia
- No clinically significant laboratory abnormalities on treatment

Possibly or Probably Related Adverse Events Occurring in ≥10% of Patients Overall

Preferred Term, n(%)	Cohort 1 150 mg N=6	Cohort 2 200 mg N=6	Cohort 3 240 mg N=6	Overall N=18
Injection site discomfort	3 (50%)	2 (33%)	3 (50%)	8 (44%)
Injection site bruising	1 (17%)	2 (33%)	2 (33%)	5 (28%)
Injection site erythema	2 (33%)	1 (17%)	1 (17%)	4 (22%)
Muscle spasms	1 (17%)	2 (33%)	1 (17%)	4 (22%)
Myalgia	2 (33%)	0	2 (33%)	4 (22%)
Injection site pain	1 (17%)	1 (17%)	1 (17%)	3 (17%)
Injection site swelling	1 (17%)	1 (17%)	1 (17%)	3 (17%)
Pain in extremity	1 (17%)	1 (17%)	1 (17%)	3 (17%)
Injection site pruritus	1 (17%)	0	1 (17%)	2 (11%)
Joint stiffness	1 (17%)	0	1 (17%)	2 (11%)
Muscle tightness	1 (17%)	0	1 (17%)	2 (11%)

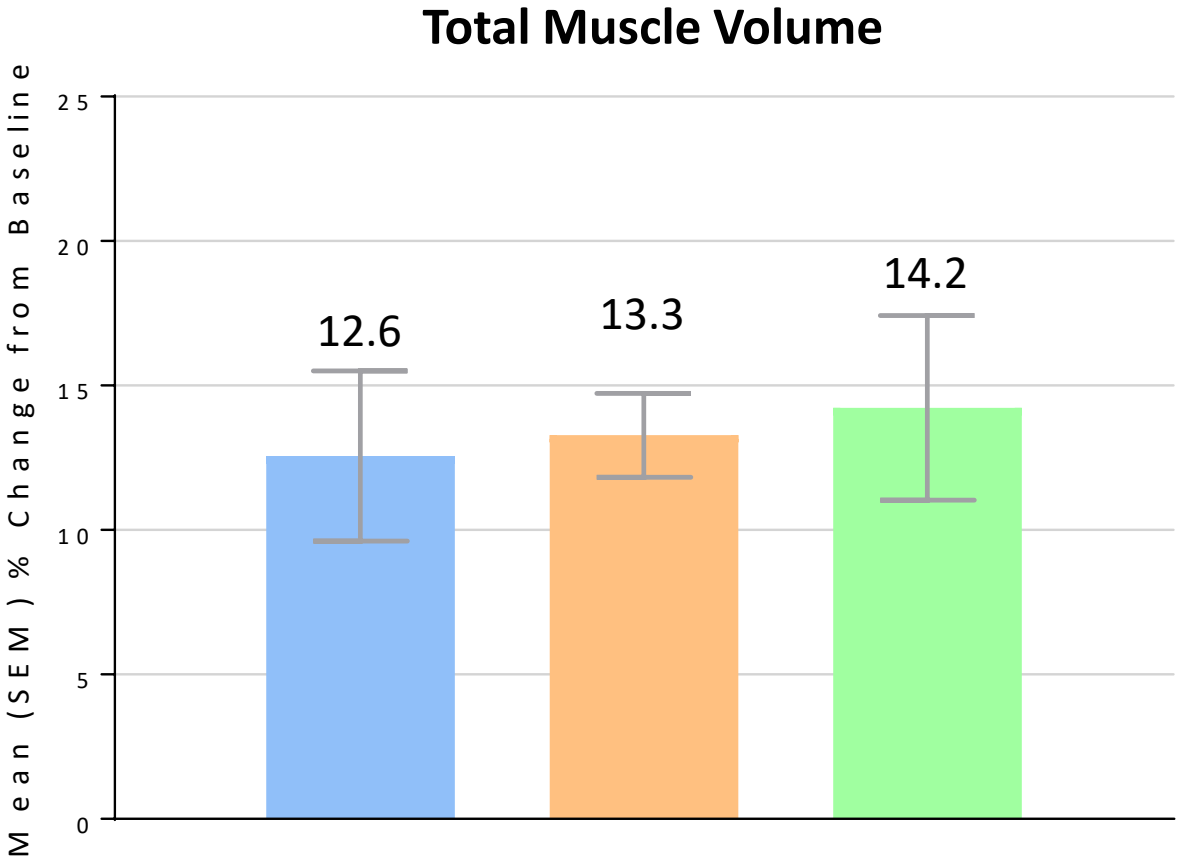
Preliminary data as of 28June2018

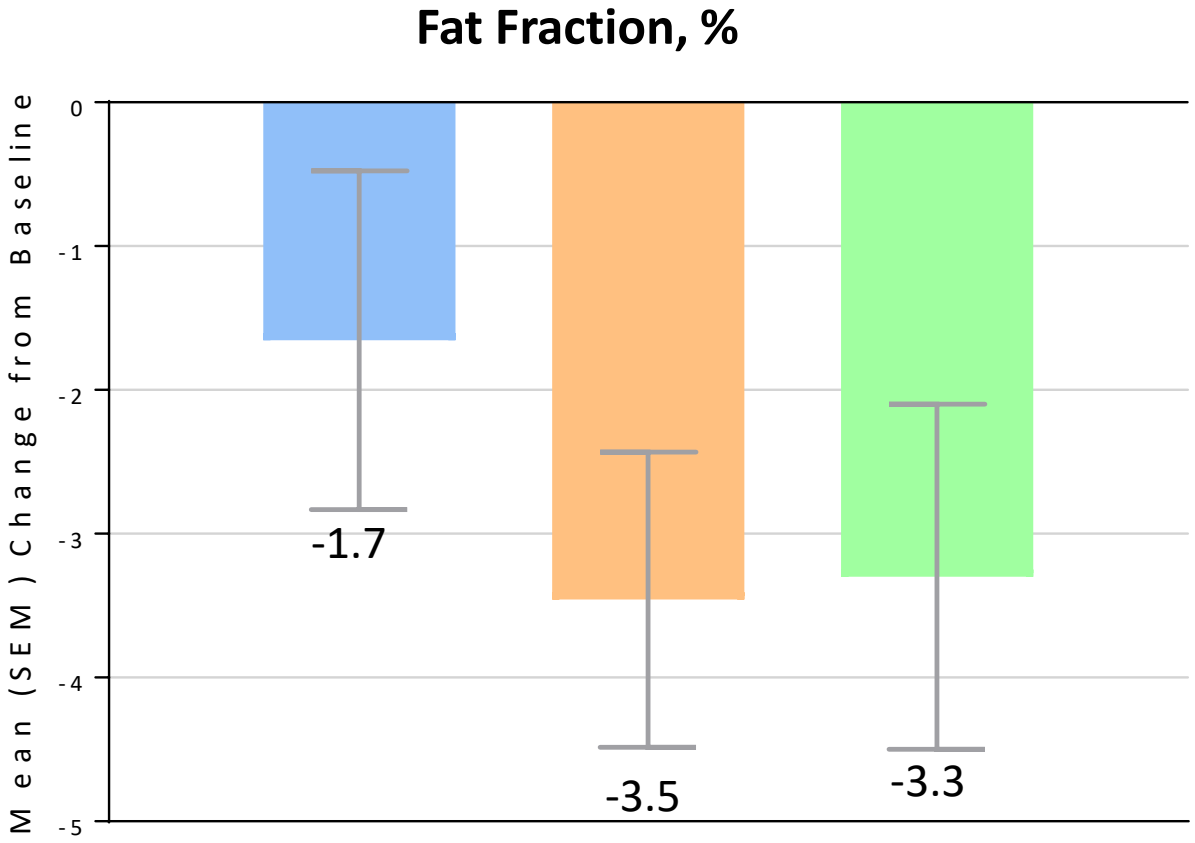
Imaging Results

ACE-083 CMT Study – Total Muscle Volume (TMV) and Fat Fraction (FF)

Part 1; Percent Change from Baseline (TMV) / Absolute Change from Baseline (FF)

- Increases in TMV observed at Day 106 (3 weeks post last dose) shown below
- Decreases in FF from overall 30% at baseline at Day 106 (3 weeks post last dose) shown below





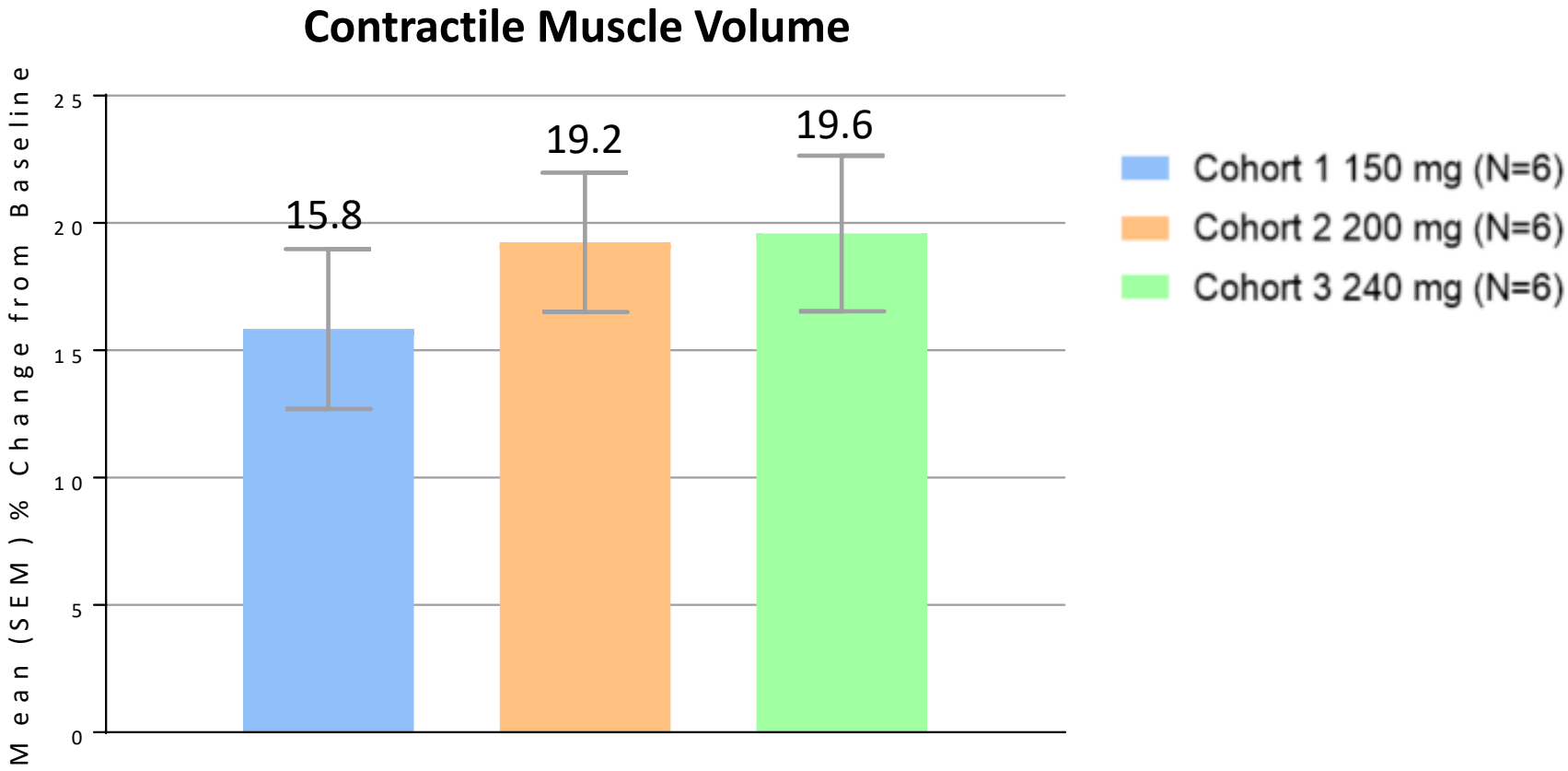
Cohort 1 150 mg (N=6)
Cohort 2 200 mg (N=6)
Cohort 3 240 mg (N=6)

Average of right and left sides
Preliminary data as of 05July2018

ACE-083 CMT Study – Contractile Muscle Volume (CMV)

Part 1; Percent Change from Baseline

- Contractile muscle volume calculated from total muscle volume and fat fraction for entire muscle
  - CMV = [TMV * (100 – fat fraction)] / 100
  - Increases in CMV observed at Day 106 (3 weeks post last dose) shown below



Average of right and left sides
Preliminary data as of 05July2018

ACE-083 CMT Study – Conclusions

- ACE-083, a locally-acting muscle therapeutic, acting on myostatin *plus* other inhibitors of muscle growth, had a favorable safety profile and was generally well-tolerated over a 3-month treatment period in patients with CMT injected in the tibialis anterior
- Changes observed in pharmacodynamic / efficacy outcome measures at 3 weeks post last dose:
  - Mean percent increases of >12% total muscle volume and >15% contractile muscle volume
  - Mean absolute decrease in fat fraction of >3% in the 200 mg and 240 mg groups
- These results support continued investigation of ACE-083 in neuromuscular diseases
  - Placebo-controlled Part 2 of this CMT study (NCT03124459) to be initiated in 2018
  - Separate Phase 2 study in FSHD is ongoing (NCT02927080)

ACE-083 CMT Study – Acknowledgments

The authors wish to thank the patients and their families for their participation and contributions as well as the following team members:

Sub-Investigators: Amy Visser, Mazen Dimackie, Georgious Manousakis, Peter Creigh, Russell Butterfield, Lauren Elman, Eric Mittelman, Nivedita Jerath, Ali Habib, Ludwig Gutmann

Clinical Evaluators: Katy Eichinger, Deanna DiBella, Melissa McIntyre, Amelia Wilson, Lindsay Baker, Keegan Kitzgerald, Jeff Schilmgen, Denise Davis, Patrick Tierney, Kyle Cunningham, Lauren Draper, Chelsea Bacon, Melissa Currence, Laura Herbelin, Ludo De Wolf, Hope Anneliese Lane, Samantha Pierre, Raphael Kupferman, Molly Stark, Sandy Swanson

Clinical Site Coordinators: Bryant Gordon, Jeanette Overton, Sonya Aziz-Zaman, Amanda Cowsert, Nicole Kressin, Ayla McCalley, Natalya Burlakova, Christine Cavallo, Janet Sowden, Diana Dimitrova

MedPace: Richard Scheyer, Georgiana Salyers, Megan Kolthoff, Taylor Meece, Stephanie Porter, Gina Kavanaugh, Emily Birkmeyer, Katie Ard, Jacob Giltrow, Elizabeth Do, Sabrina Lesh, Courtney Pearce, Leslie Foertsch

Acceleron: Leah Leahy, Jade Sun, Saba Qamar, Connie Slocum, Carrie Barron, Shuree Harrison, Thienhuu Nguyen, Suada Celikovic

VirtualScopics, BioSensics, ERT