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Accelerating Drug Discovery to Transform Patients' Lives

CMT Overview and ACE-083 Phase II Trial Webinar

April 3, 2017

Acceleron Forward-Looking Statements

This presentation contains forward-looking statements about the Company's strategy, future plans and prospects, including statements regarding the development compound ACE-083 program generally, the timeline for clinical development and regulatory approval of the Company's compounds, the expected timing for the reporting of data from ongoing trials, and the structure of the Company's planned or pending clinical trials. The words “anticipate,” “appear,” “believe,” “continue,” “could,” “estimate,” “expect,” “forecast,” “goal,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

Each forward-looking statement is subject to risks and uncertainties that could cause actual results to differ materially from those expressed or implied in such statement. Applicable risks and uncertainties include the risks that the Company's cash, cash equivalents and investments will be insufficient to fund operations into the second half of 2019, that preclinical testing of the Company's compounds and data from clinical trials may not be predictive of the results or success of ongoing or later clinical trials, that data may not be available when the Company expects it to be, that the Company or its collaboration partner, Celgene, will be unable to successfully complete the clinical development of the Company’s compounds, that the development of the Company's compounds will take longer or cost more than planned, that the Company or Celgene may be delayed in initiating, enrolling or completing any clinical trials, and that the Company's compounds will not receive regulatory approval or become commercially successful products.

Other risks and uncertainties include those identified under the heading "Risk Factors" included in the Company's Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on March 1, 2017, and other filings that the Company has made and may make with the SEC in the future. The forward-looking statements contained in this presentation reflect the Company's current views with respect to future events, and the Company does not undertake and specifically disclaims any obligation to update any forward-looking statements.

Agenda

Introduction

- Habib Dable
  Chief Executive Officer

CMT Overview

- David Walk, M.D.
  Associate Professor of Neurology

  Director, ALS and CMT Centers of Excellence, University of Minnesota Medical Center

ACE-083 Overview

- Matthew Sherman, M.D.
  Chief Medical Officer

CMT Phase 2 Trial Design

- Kenneth Attie, M.D.
  Vice President, Medical Research

Question & Answer Session

Neuromuscular Disease
Habib Dable
Chief Executive Officer

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CMT Overview

David Walk, M.D.
Associate Professor of Neurology
Director, ALS and CMT Centers of Excellence
University of Minnesota Medical Center

Topics Covered

- Biography – Areas of Research, Practice Overview
- Spectrum of Neuromuscular Disorders
- Patient Population
- Genetics
- Clinical Presentation
- Current Standard of Care
- Outcome Measures
- Drug Development Landscape – Past/Present
- Summary

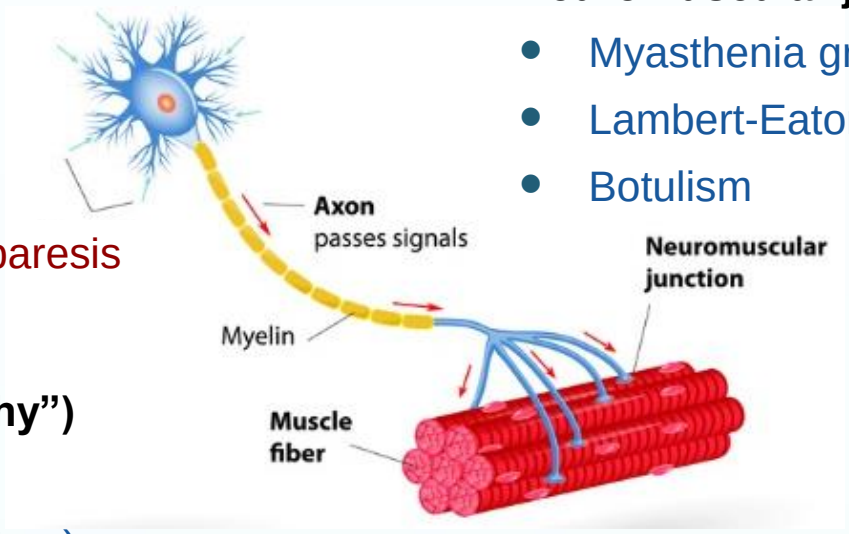
Biography

- **Training**
  - Medical school: Brown University
  - Neurology training: University of Chicago
- **Practice**
  - University of Illinois at Chicago 1990-1999
  - University of Minnesota 1999-present
    - Division Director, Neuromuscular Medicine, Department of Neurology
- **Areas of interest**
  - Small fiber neuropathy
  - Neuropathic pain
  - ALS
  - CMT

Spectrum of Neuromuscular Disorders

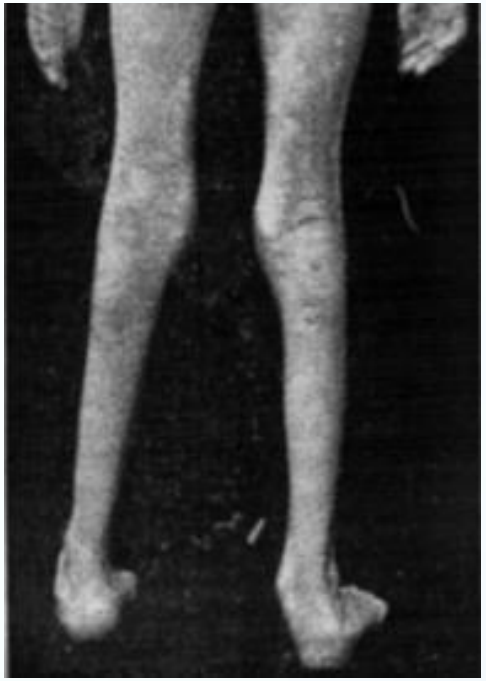
Hereditary
Non-hereditary (“acquired”)

- **Motor neuron disease**
  - Sporadic ALS
  - Familial ALS
  - Polio
  - Hereditary spastic paraparesis
- **Nerve disease (“neuropathy”)**
  - CMT (axon or myelin)
  - CIDP (myelin, inflammatory)
  - Toxic, metabolic, or nutritional (axon)
    - e.g., diabetes, chemotherapy
  - Inflammatory (axon)



- **Neuromuscular junction disease**
  - Myasthenia gravis
  - Lambert-Eaton
  - Botulism
- **Muscle disease (“myopathy”)**
  - Muscular dystrophies
  - Congenital
  - Channelopathies
  - Mitochondrial
  - Metabolic, toxic, inflammatory
  - Medical conditions

Charcot-Marie-Tooth (CMT) Disease



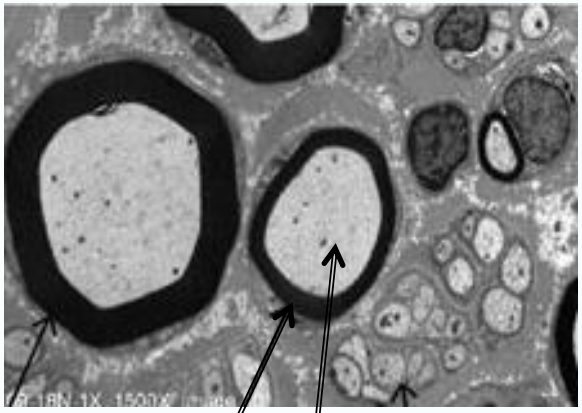
- The most common inherited neurologic disorder
  - Prevalence estimated at 1:2,500 or >100K in US
  - Also called hereditary motor and sensory neuropathy (HMSN)
- Currently over 100 different identified mutations
- Affects myelin sheath of nerve or nerve axon
- Onset typically in second decade of life
- Leads to slowly progressing muscle weakness
  - Affects hands and feet first
  - Diagnosis is based on
    - clinical presentation
    - genetic testing
- Leads to substantial morbidity

CMT Classification: Major Categories

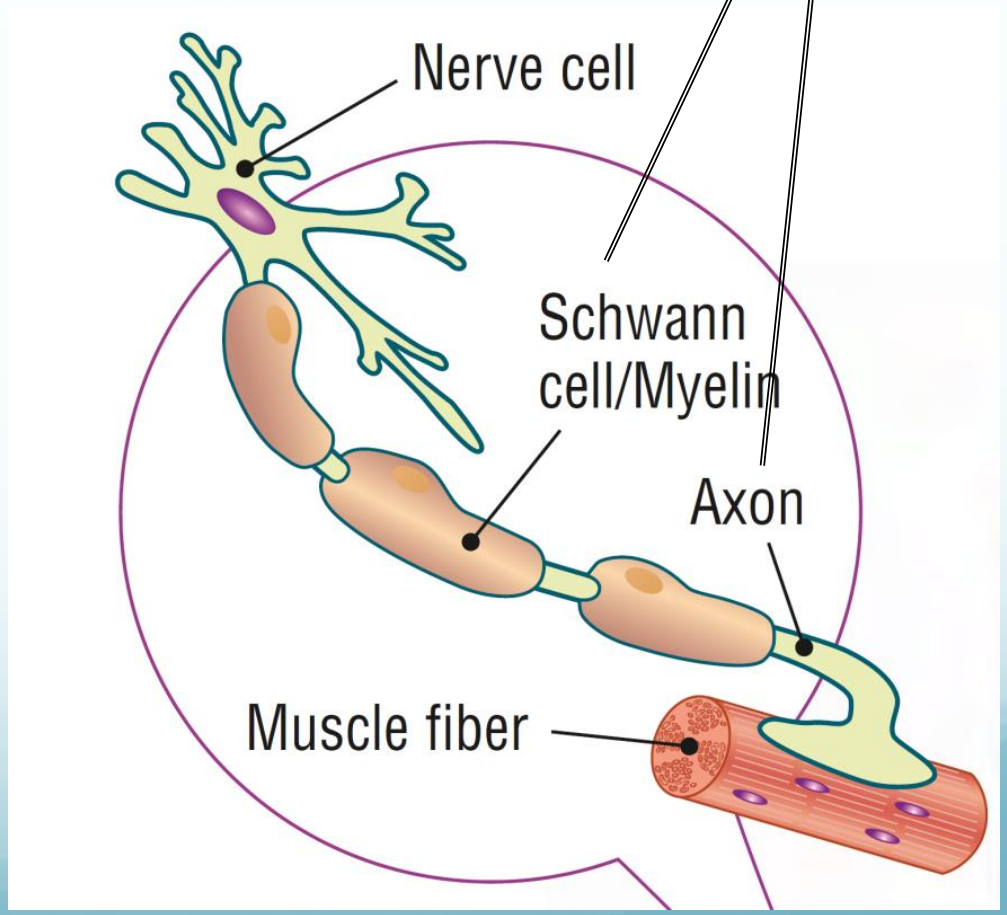
Type	Inheritance	Structure Affected	Estimated Frequency
CMT1	dominant	myelin	60%
CMT2	dominant	axon	20%
CMTX	X-linked	usually myelin	10%
CMT4	recessive	usually myelin	5%

Subtypes (CMT1A, 2A, X1, etc.) represent individual genes affected

CMT mutations involve a variety of structural and functional proteins

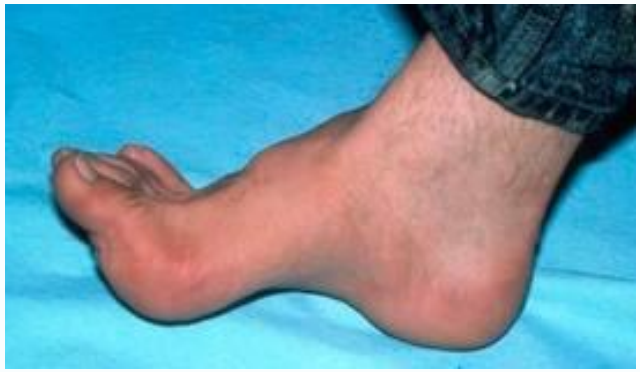


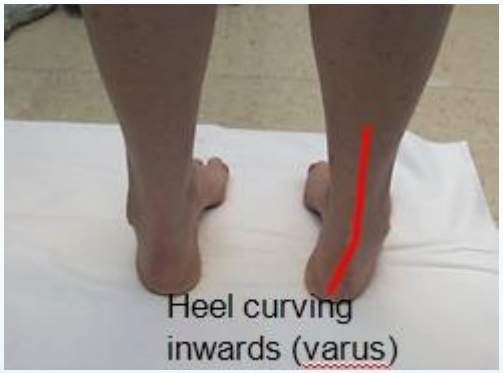
- **Myelin proteins**
  - *PMP22*
  - *MPZ*
  - *GJB1*
- **Axonal proteins**
  - Protein transport
    - *LITAF*
  - tRNA synthesis
    - *GARS, YARS*
  - Mitochondrial function
    - *MFN2, GDAP1*
  - Lysosomes
    - *SH3TC2, RAB7, FIG4*

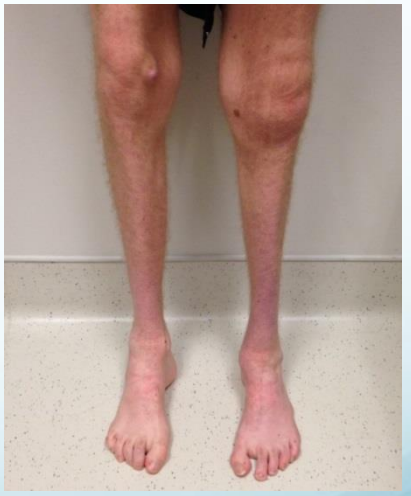


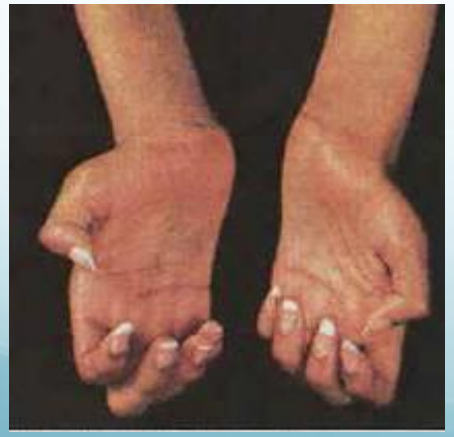
CMT - Physical Appearance

- Foot deformities
  - Intrinsic foot muscle weakness
  - High arched foot (pes cavus)
  - Hammer toes
  - Heel inversion (varus)
- Calf atrophy
- Foot drop
- Hand muscle involvement
  - Claw hand









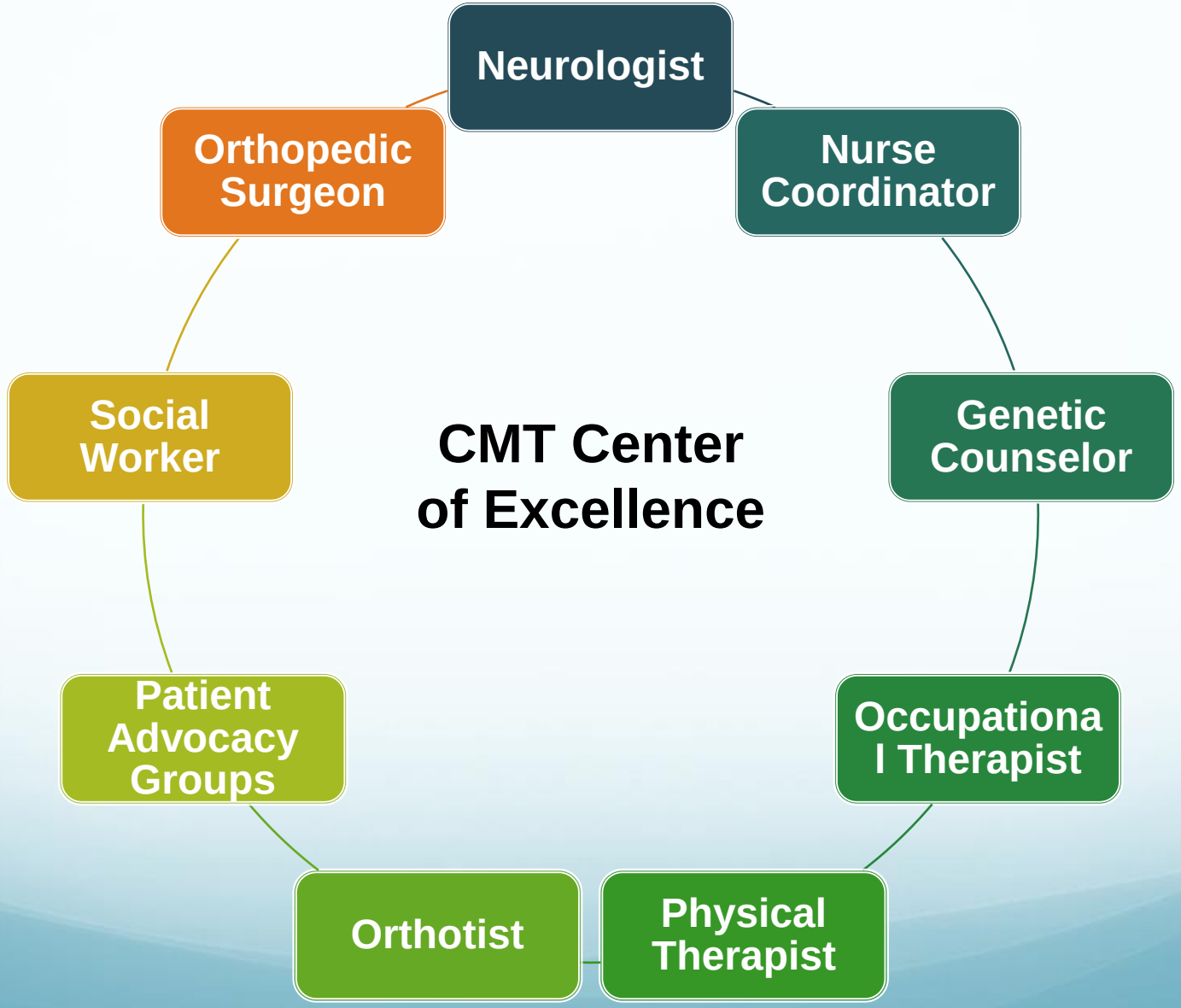
Clinical Presentation of CMT1

- Symmetric weakness of feet and ankles
  - Ankle sprains
  - Foot drop
  - Frequent falls
  - Difficulty walking and inability to run
- Loss of sensation
  - Injuries, skin breakdown, dropping objects
  - Numbness
  - Position sense
- Gait instability
  - Muscle weakness
  - Loss of sensation
  - Loss of balance, falls
- Loss of dexterity
  - Difficulty buttoning, writing, using utensils, operating machinery
- Fatigue
- Musculoskeletal pain, muscle cramps

Clinical Presentation of CMTX

- Asymmetric weakness of feet, legs, and hands
  - Muscle cramps
  - Ankle sprains
  - Difficulty running and walking
  - Foot drop
  - Falls
  - Difficulty writing, using utensils, operating machinery
- Males more affected

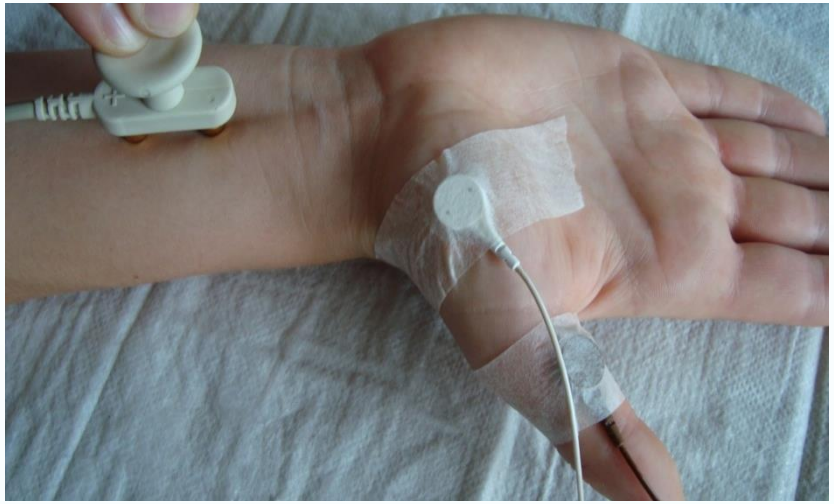
Multidisciplinary Care

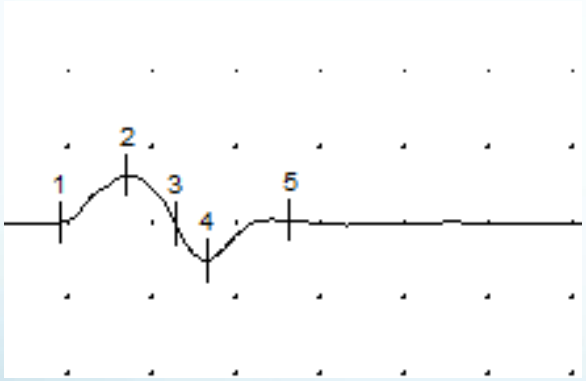


Neurologist Assessment

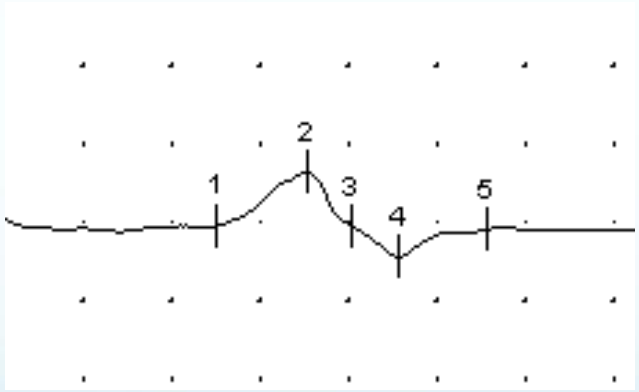
- Identify the patient's goals
- Make a diagnosis, based upon:
  - Symptoms
  - Examination (sensation, muscle function, reflexes)
  - Nerve conduction testing
  - Genetic testing
- Educate
  - Prognosis
  - Management
  - Research
  - Patient advocacy groups
- Refer as appropriate to therapists

Nerve Conduction Testing

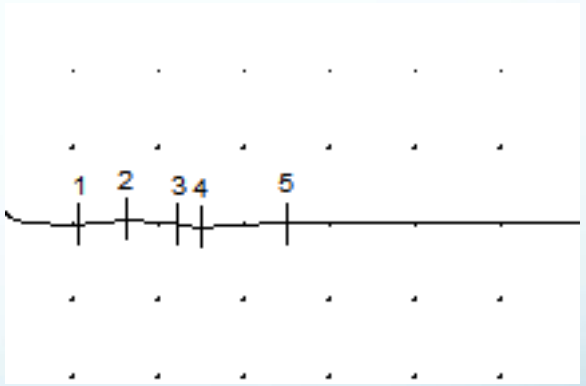




Normal



- **Slow conduction**
- **Abnormal myelin**
- **CMT1**



- **Low amplitude**
- **Normal conduction**
- **Axon loss**
- **CMT2**

Genetic Assessment

- Obtain family history
- If gene is known in a family member:
  - Perform neurologic examination
    - If abnormal and no other nerve disease, likely to be CMT
    - Can confirm by testing for known mutation
- If gene is not known in a family member:
  - Nerve conduction test indicates CMT1
    - Test for CMT1A
    - If negative, test all CMT1 genes
    - If negative, consider whole genome sequencing
  - Nerve conduction test indicates CMT2
    - Test all CMT2 genes
    - If negative, consider whole genome sequencing

Physical/Occupational Therapy

- **Assessment**
  - Pain
  - Range of motion
  - Strength
  - Gait and balance*
  - Fall risk assessment*
  - Cognitive assessment if indicated
- **Living environment**
  - Patient concerns
  - Barriers (stairs, tub, etc)
  - Assistance needs
  - Equipment
    - For mobility
    - For activities of daily living
  - Driving

Walking speed, standing balance, and fall risk are influenced by ankle strength

Orthotics Assessment

- Assessment of limb function
- Identifying needs for stabilization in all motions at ankle
  - Multiple devices available
- Custom modifications to braces
  - Often uncomfortable and not well tolerated

Clinical Research - Outcome Measures

Outcome	Domain
MRI (muscle volume, intramuscular fat volume)	biomarker
Nerve conduction studies	biomarker
Manual muscle testing	strength
Hand-held dynamometry/fixed system	strength
6-Minute walk test	motor function
10-Meter walk/run	motor function
Overall Neuropathy Limitations Scale (ONLS)	disability
CMT Neuropathy Score / CMT Examination Score	combination
CMT Health Index (Univ of Rochester)	PRO

Drug Development

- Current
  - Pharnext (PXT3003) – a fixed combination pleodrug comprising low doses of baclofen, naltrexone hydrochloride and sorbitol
    - Down-regulates the overexpression of PMP22 gene
    - Phase 2 results in 80 patients
    - Initiated Phase 3 trial in December 2015 in 300 CMT1A patients
  - Others
    - Pre-clinical stage or earlier

Potential Treatment Strategies

- Reduce expression of PMP22 in CMT1A
- Alter impact of impaired proteins
- Identify modifier genes and their functions
- Identify epigenetic modifiers

CMT - Summary

- The most common inherited neurologic disorder
- Most prominent disability is foot and hand weakness
  - Results in impaired gait, impaired stance, and falls
- No effective treatment of disease process to date
- Treatment is symptom and disability management
  - Ankle brace commonly used but often poorly tolerated

ACE-083 in Neuromuscular Diseases:

Matthew Sherman, M.D.
Chief Medical Officer

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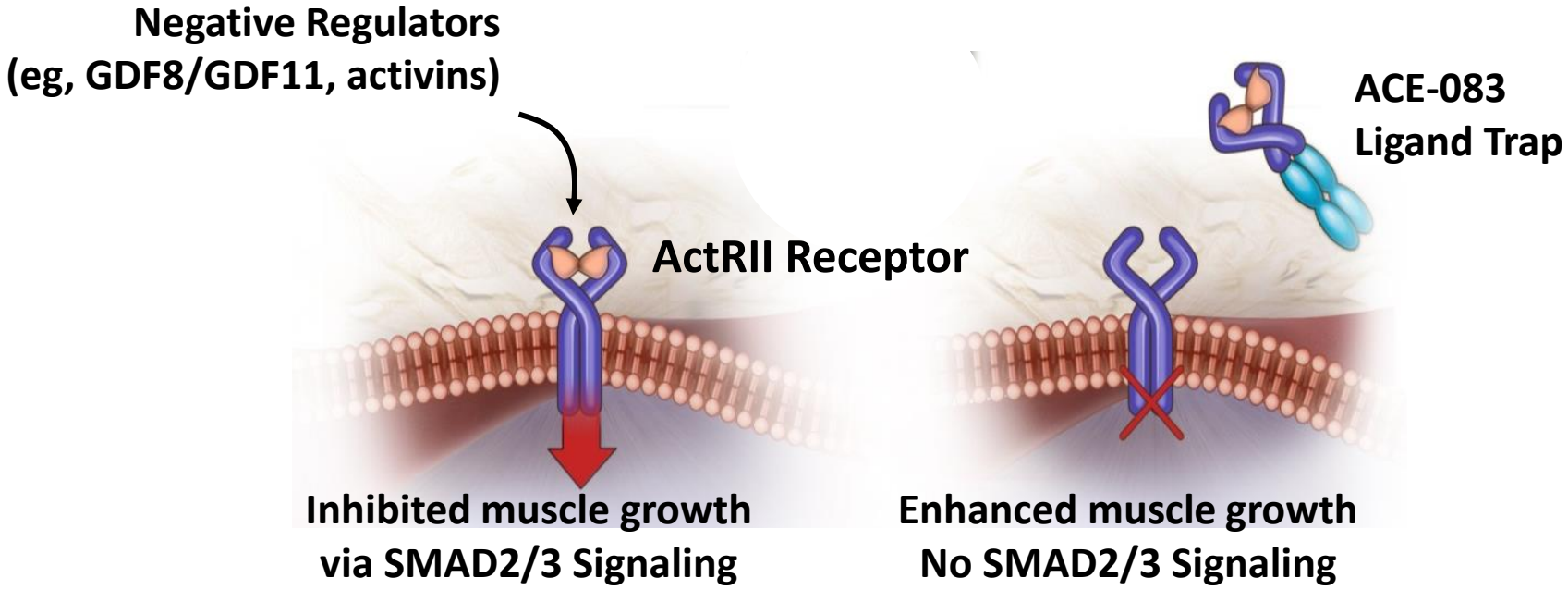
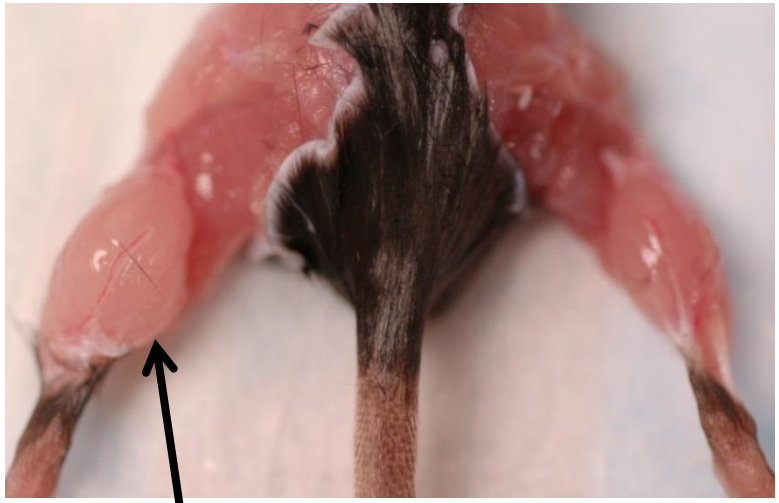
ACE-083 – A Local Muscle Therapeutic

- **ACE-083** is a locally acting protein therapeutic that binds GDF8 and other negative regulators of skeletal muscle growth in the TGF-β superfamily
  - ACE-083 was designed to increase muscle mass and strength selectively in the muscle into which the drug is administered

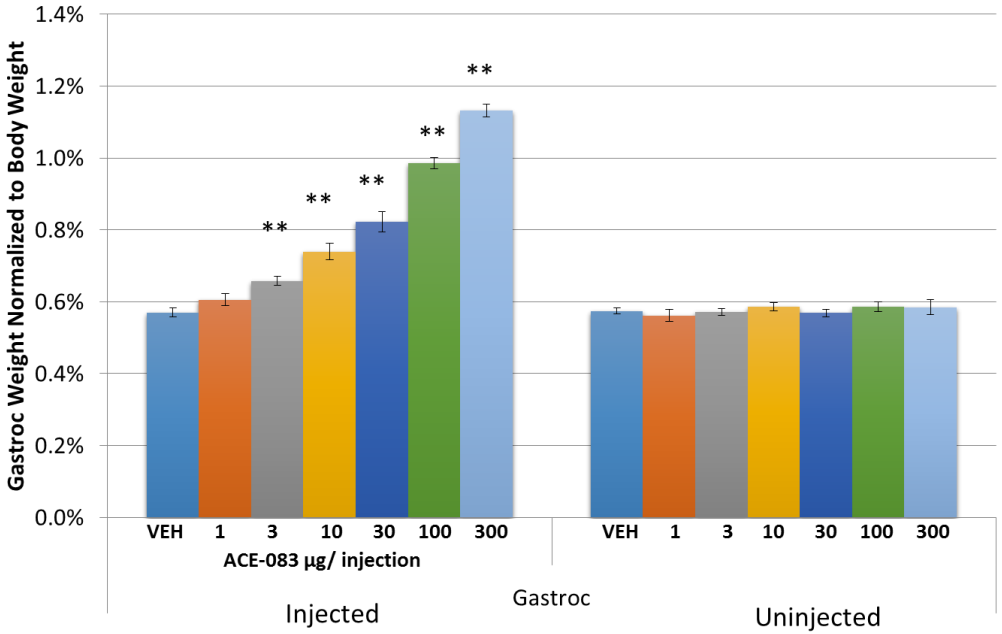


ACE-083 Increased Muscle Mass Locally in Wild Type Mice

- In wild type (WT) mice dosed 2x/week for 1 month into the left gastrocnemius muscle, ACE-083 increased muscle mass locally in the target muscle in a dose dependent fashion



ACE-083 injected



**p<0.05 vs vehicle and vs uninjected leg

World Muscle Society presentation, 2014

ACE-083 Increases Muscle Fiber Cross-sectional Area and Tetanic Force of Tibialis Anterior Muscle in Disease Models

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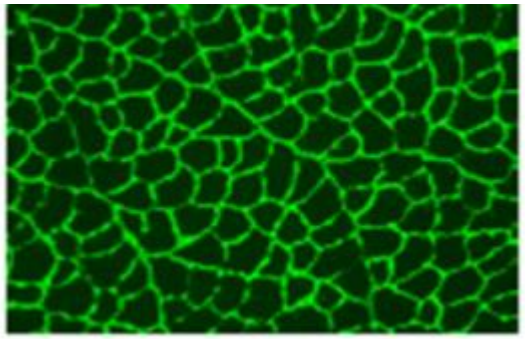
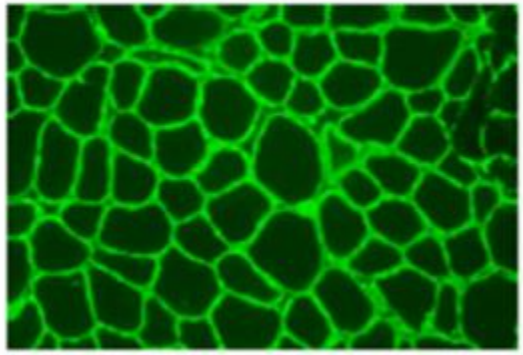
Increased Muscle Size

Uninjected Tibialis Anterior



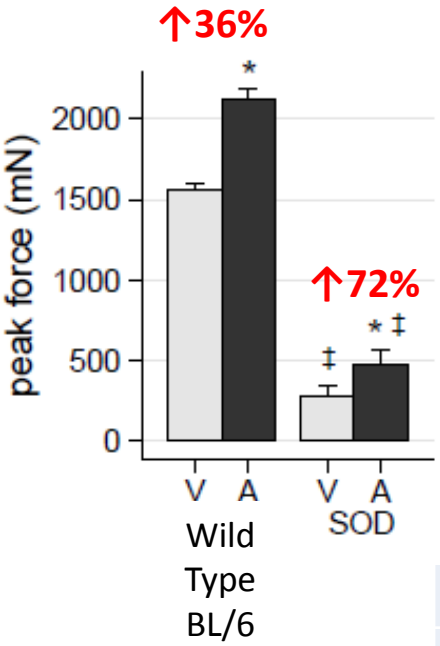
Injected Tibialis Anterior



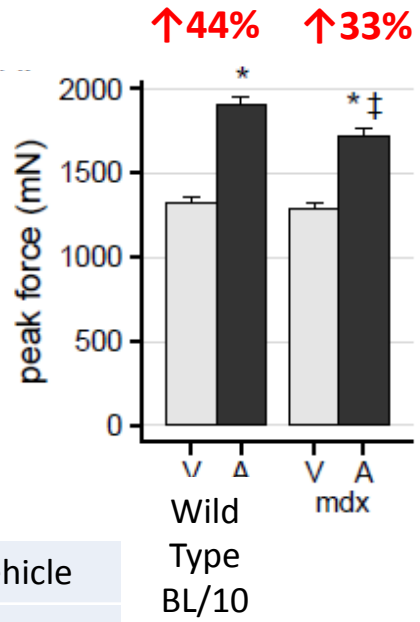
Increase in Fiber Cross Sectional Area / Muscle Hypertrophy

Increased Muscle Strength

ALS Mouse Model



DMD Mouse Model



V = Vehicle

A = ACE-083

* indicates a significant difference from the vehicle treated group of the same genotype.

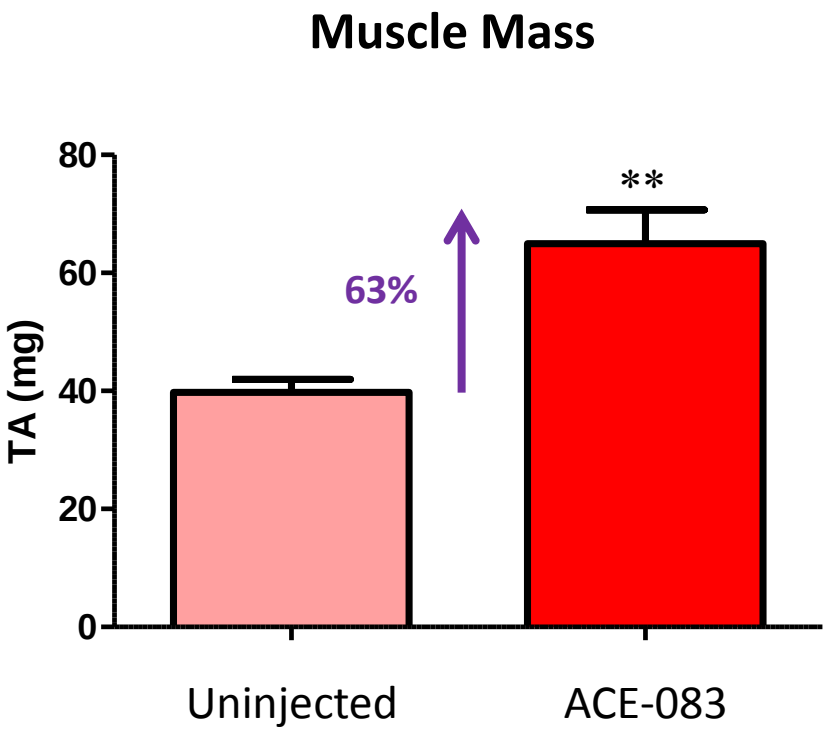
‡ indicates a significant difference vs. WT mice of the same treatment combination.

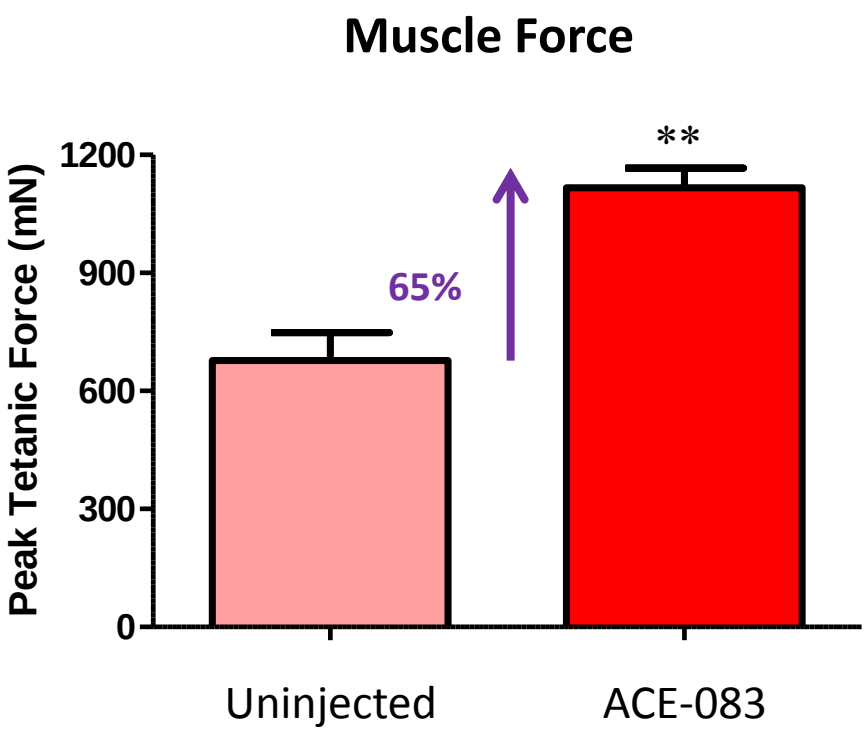
CMT Mouse Model

- "Trembler Jackson" (Tr-J) mouse is a model of CMT1
  - Spontaneous mutation in peripheral myelin protein 22 (Pmp22)
  - Delayed myelination followed by hypermyelination and demyelination

- Mice with established disease were treated by direct injection in the right tibialis anterior (TA) muscle 2X/week for 4 weeks

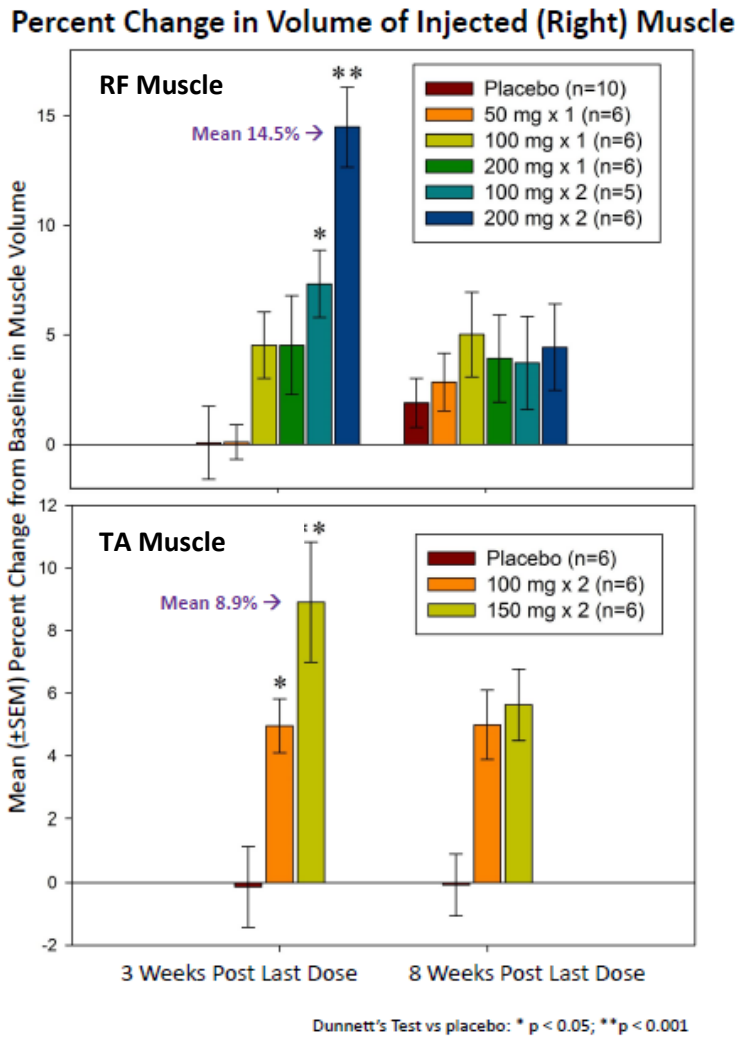
ACE-083 Increases TA Muscle Mass and Strength in a Mouse Model of CMT

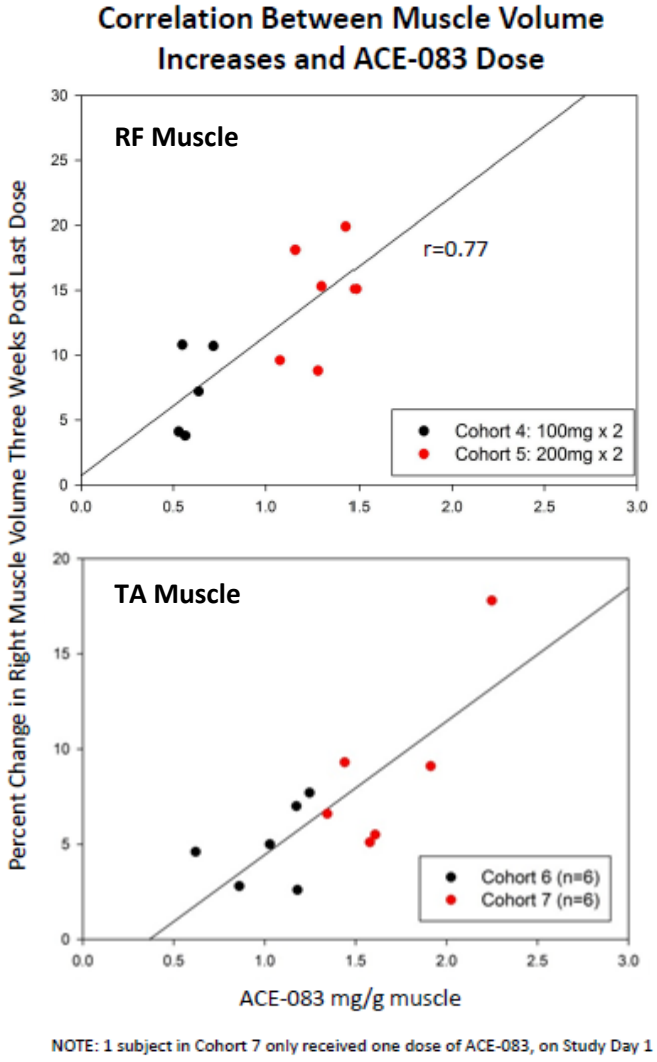




N=5 /group ** p<0.001

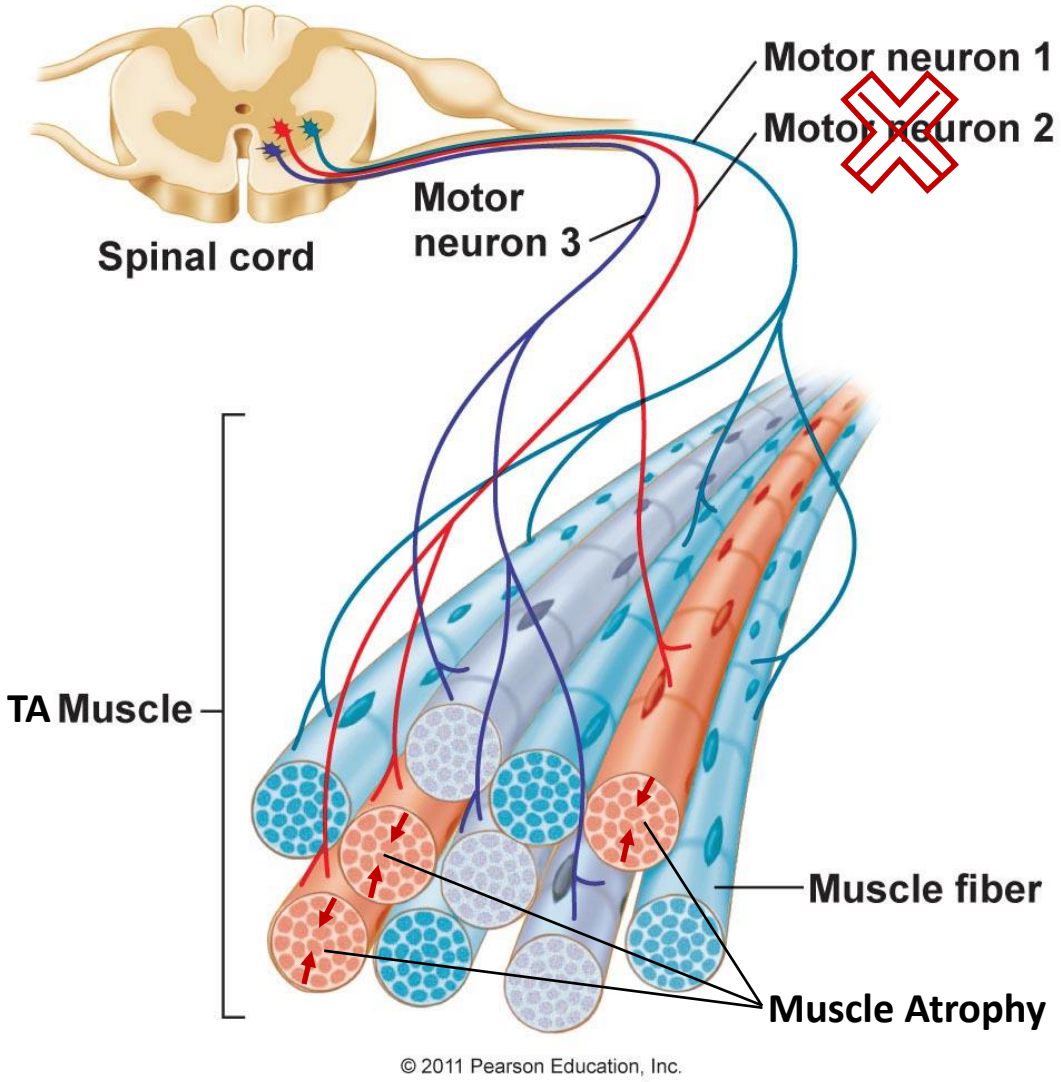
ACE-083 Produced Substantial Dose-Dependent Increases in Muscle Volume in a Phase 1 Study





RF = Rectus Femoris
TA = Tibialis Anterior

Our Goal in CMT/Neurologic Diseases



Partial denervation of muscle

↓

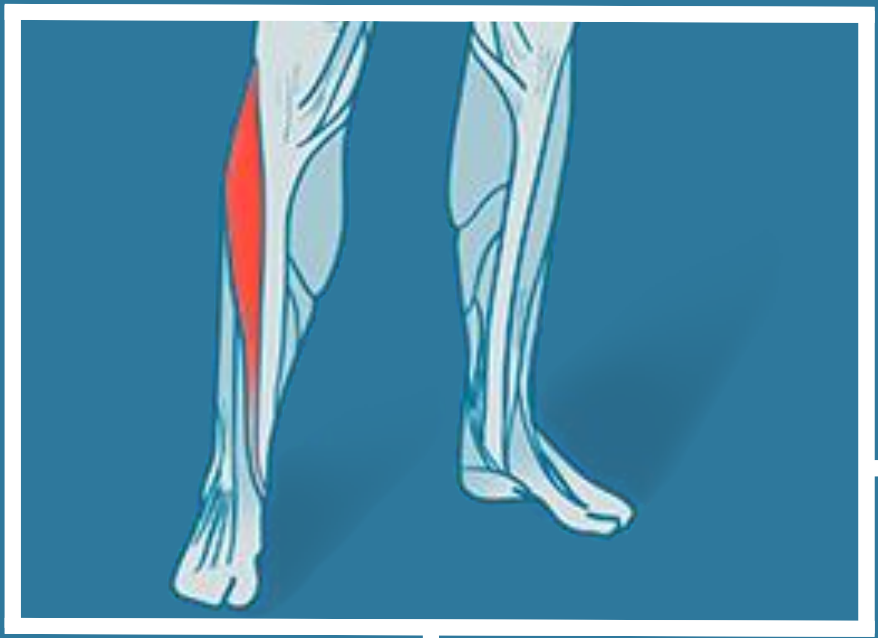
Specific muscle weakness

↓

ACE-083 treatment

↓

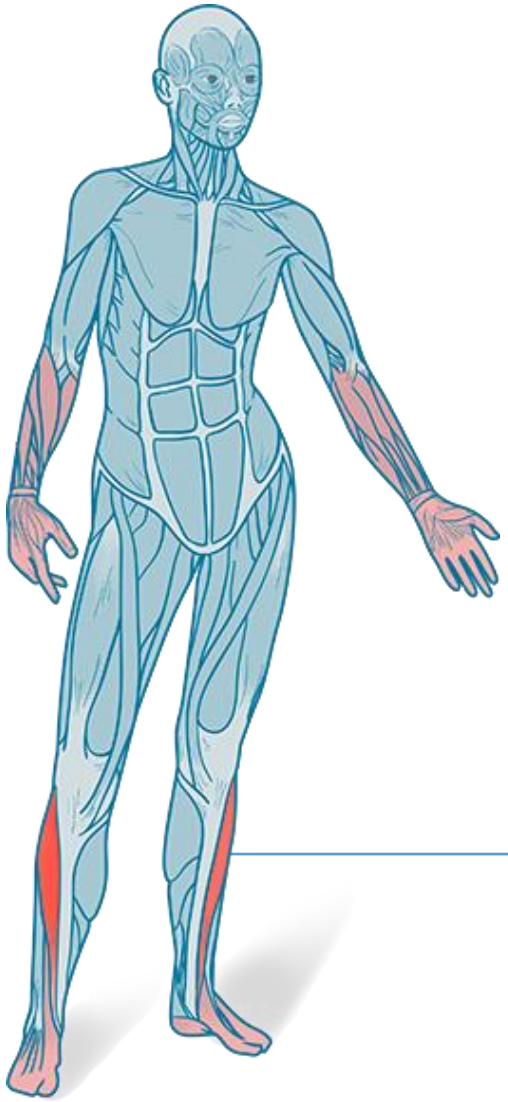
Increased residual muscle volume and strength



Kenneth Attie, M.D.
VP, Medical Research

Phase 2 Study in CMT

ACE-083 Targeted Muscle Therapy in CMT

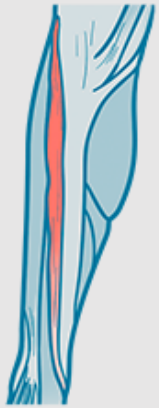


Weakness of the Tibialis Anterior (TA)

- Causes foot drop
- Impairs mobility/walking
- Increases risk of falls

Tibialis Anterior

Strengthening the TA muscle should alleviate foot drop and improve ambulation and stair-climbing ability

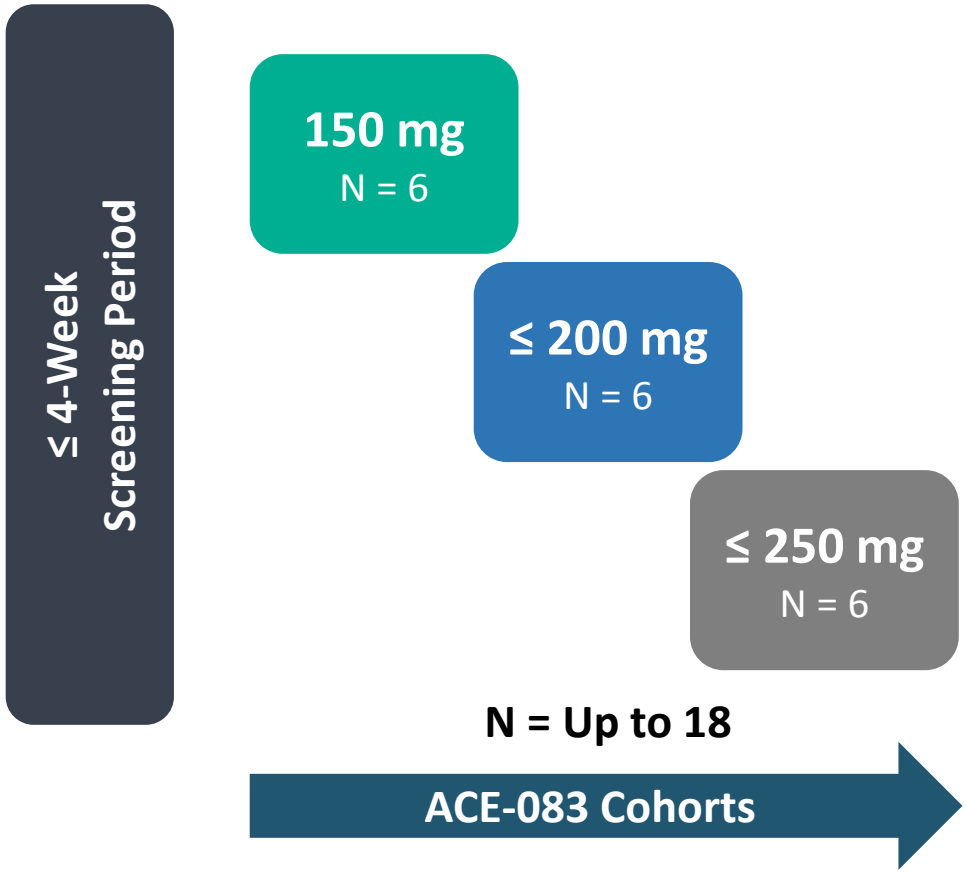


Phase 2 CMT Study - Key Eligibility Criteria

- Age ≥ 18 years
- Genetically-confirmed CMT1 or CMTX, or, confirmed first-degree relative and clinical signs/symptoms of CMT1 or CMTX
- Six-minute walk distance ≥ 150 meters
- Independent ambulation ≥ 10 meters
- Left and right ankle dorsiflexion weakness
- No severe deformity or fixation of ankle

ACE-083 CMT Study Design - Part 1

Part 1: non-randomized, open-label, dose-escalating with goal to identify dose to be used in Part 2 of this two-part clinical trial



Objectives

- Safety & tolerability
- Determine dose for Part 2
- Increase in injected muscle volume by MRI
- Improvement in strength of injected muscle
- Improvement in function of injected muscle and health-related quality of life

ACE-083 CMT Study Design - Part 2

Part 2: randomized, double-blind, placebo-controlled

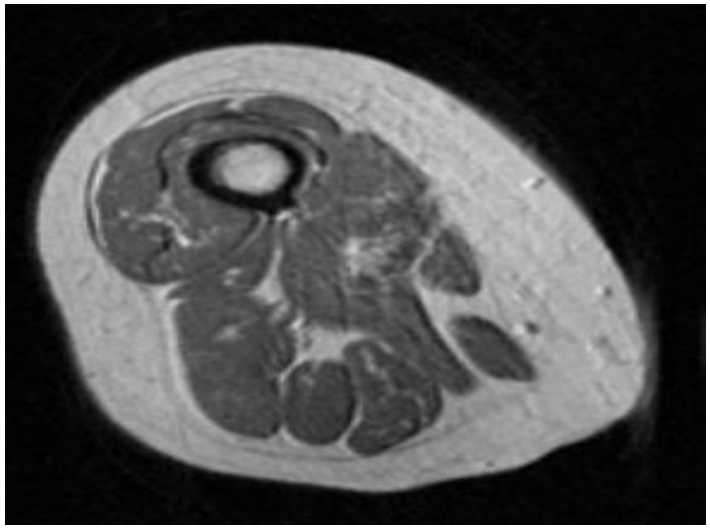
Treatment Duration:
3 months / up to 5 doses

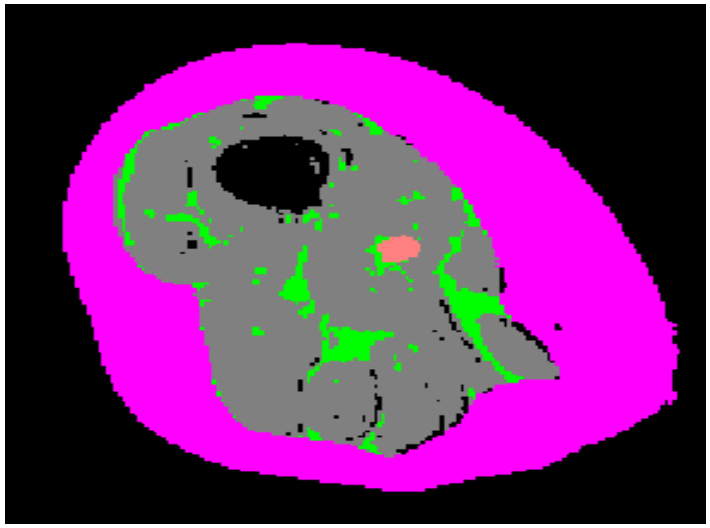
N = 24

Muscle Volume and Fat Fraction by MRI

- **Percent change from baseline in muscle volume of tibialis anterior by MRI**

MRI Imaging





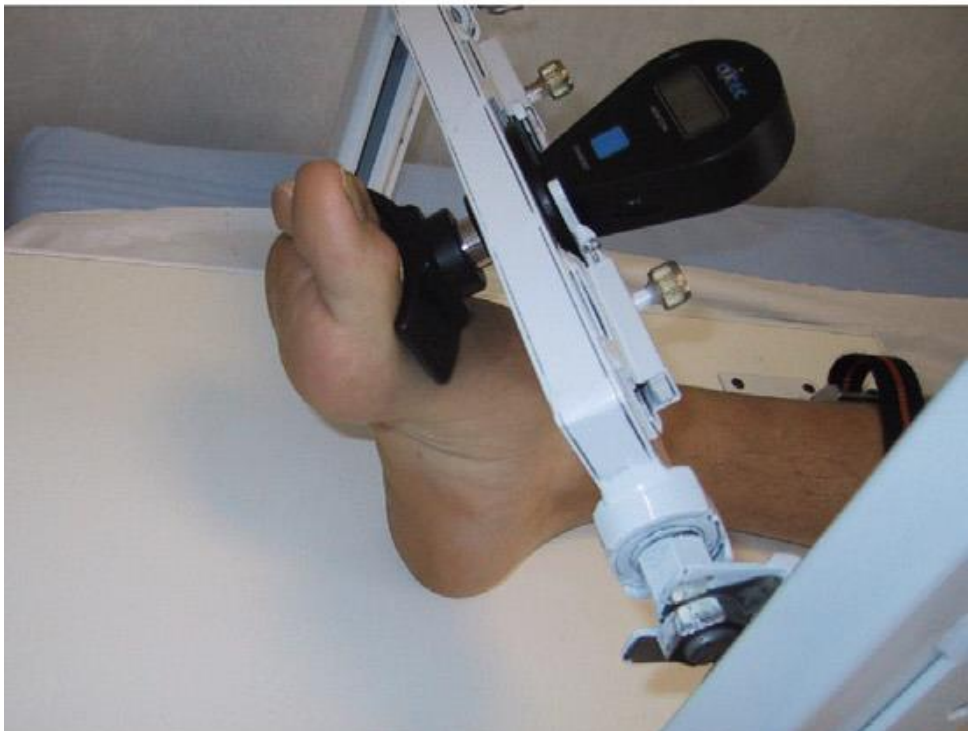
Grey = Muscle
Pink = SC fat
Green = IM fat

Not actual ACE-083 trial imaging

Tibialis Anterior Strength Measurements in CMT Study

- **Percent change from baseline in strength of tibialis anterior by quantitative muscle testing**

Strength Measurements



Solari A, et al. Neuromuscular Disorders 2008;18:19-26

Functional Assessments

- **Tests of function for tibialis anterior muscle**
  - 10 meter walk/run
  - 6 minute walk test (6MWT)
  - Gait analysis
  - Berg balance scale

- **Physician- and Patient-Reported Outcome (PRO) Measures**
  - CMT Examination Scale v.2 (CMTES2)
  - CMT Health Index (CMT-HI)

CMT Key Takeaways

- CMT is a slowly progressive neurologic disease
  - Tibialis anterior (TA) weakness can start in childhood and persist into the later decades of life
  - ACE-083 is designed to increase muscle volume and strength in target muscles
- Encouraging results from CMT and ALS neuropathy mouse models
- Data from Phase 1 study demonstrated safety and unprecedented increases in muscle volume in the TA as well as quadriceps
- Functional endpoints are well established for the lower extremity and can be supplemented by gait analysis and PRO tools

ACE-083 CMT Q&A Session

David Walk, M.D.	University of Minnesota Medical Center
Habib Dable	Chief Executive Officer
Matthew Sherman, M.D.	Chief Medical Officer
Kenneth Attie, M.D.	VP, Medical Research
Todd James, IRC	Investor Relations and Corp. Comm.

Thank You

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