BMS-986089: An Anti-Myostatin Adnectin Targeting Duchenne Muscular Dystrophy

Leslie Jacobsen, MD
Medical Lead
On Behalf of the BMS Anti-Myostatin Team
PPMD Webinar
March 30, 2016

Bristol-Myers Squibb

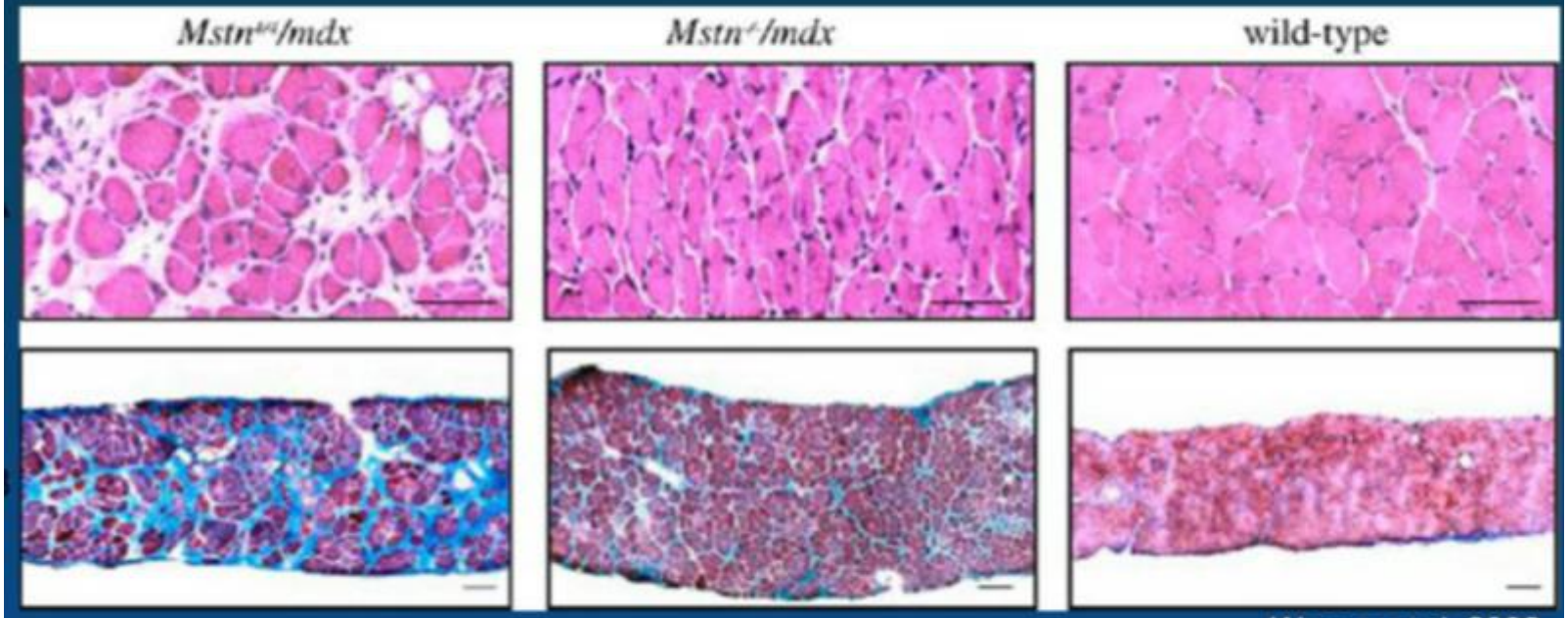
BMS-986089: an Anti-Myostatin Adnectin

- BMS-986089 is a fully human anti-myostatin adnectin
- Sub nM affinity for myostatin, supporting subcutaneous dosing
- Being developed as a treatment for Duchenne Muscular Dystrophy
- Ongoing study of BMS-986089 in boys with Duchenne

Myostatin: A Negative Regulator of Muscle Growth

- Myostatin (GDF-8) discovered as novel member of TGF-β superfamily
- Removal of the myostatin gene in mice (knock-out):
  - 2-3x increase in body weight, widespread increase in skeletal muscle
  - Decreased fat mass, increased bone density
  - No increase in cardiac muscle
- Myostatin gene sequence and function is conserved across species; knockout produces a similar phenotype in:
  - Mice, Cattle, Sheep, Zebrafish, Dog, & Human

Genetic ablation of myostatin improves muscle architecture in *mdx* mouse



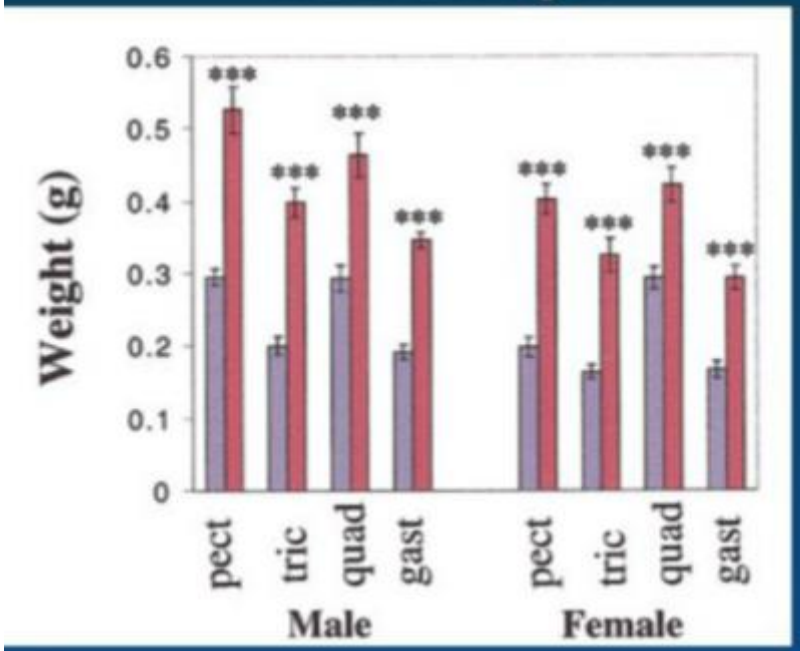
Wagner et al, 2002

A: H & E staining: myostatin KO increases muscle development in mdx diaphragm

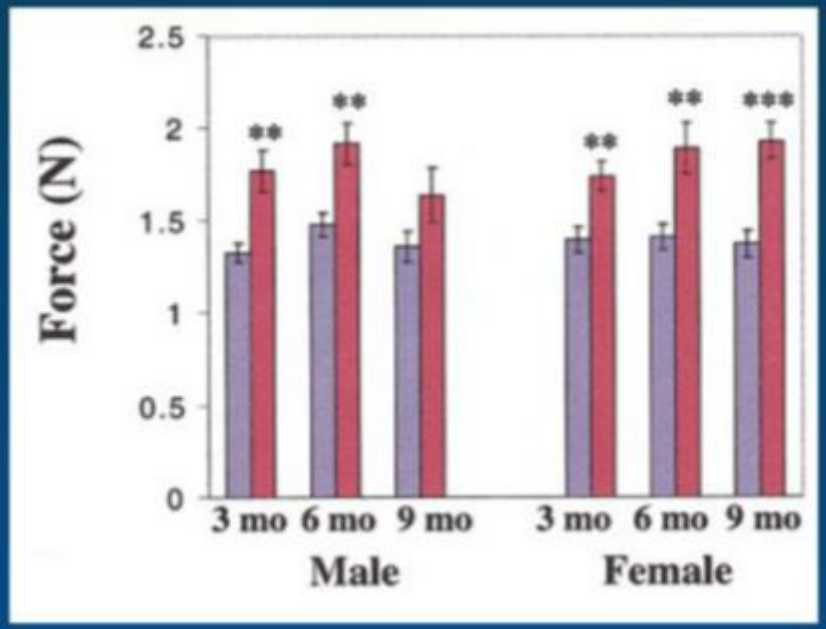
B: Basson's trichrome staining: myostatin KO decreases fibrosis in mdx diaphragm

Genetic ablation of myostatin improves phenotype of *mdx* mouse – a mouse model of DMD

Muscle weight



Forearm grip strength



mdx

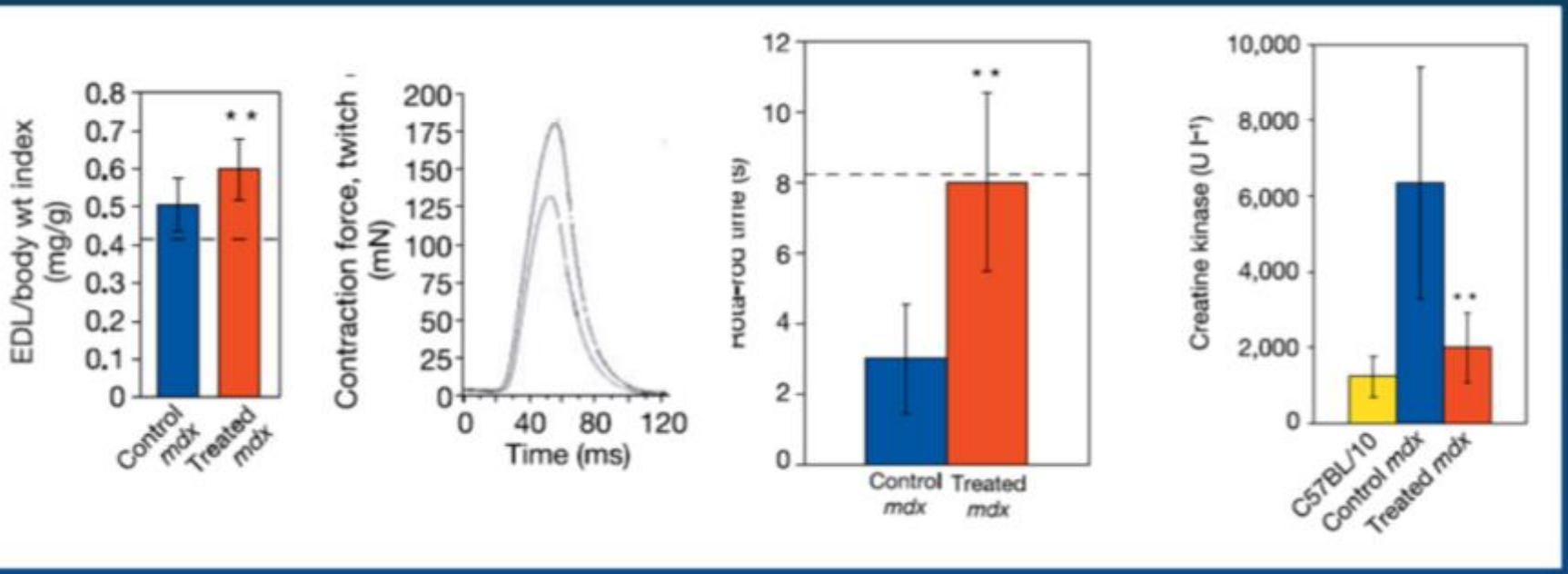
mdx/myo KO

Muscle weight and grip strength are increased in myostatin knock-out mice crossed with *mdx* mice

Wagner et al., 2002

Anti-myostatin antibody treatment improves phenotype of *mdx* mouse

Muscle Weight | Muscle Strength | Rotorod Performance | Serum Creatine Kinase



Weekly subcutaneous treatment for 3 months with an anti-myostatin antibody increased muscle weight and strength, improved locomotor performance and decreased serum creatine kinase in *mdx* mice

Bogdanovich, Nature, 2002

Topline toxicology findings

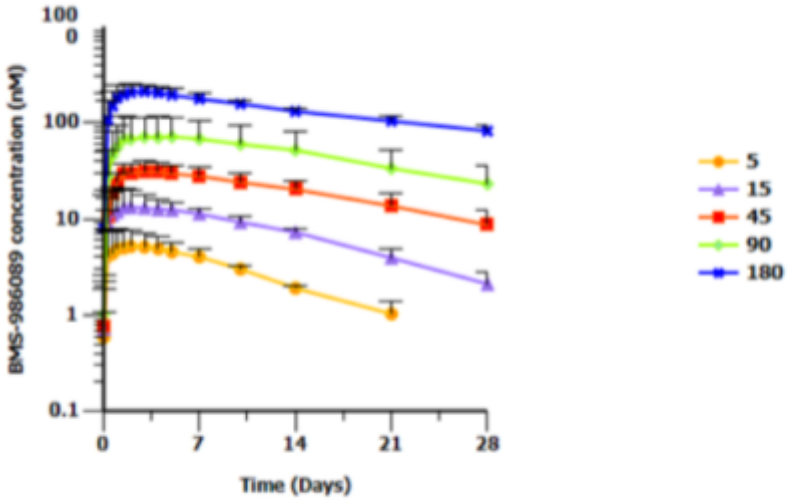
- BMS-986089 was well tolerated in all rat and monkey toxicology studies
  - 6 month rat & monkey chronic tox studies
  - 12-wk juvenile male rat study
- Evidence of pharmacodynamics efficacy in tox studies:
  - 12-wk juvenile male rat study:
    - Increases in body and leg muscle weight and dose dependent increases in trabecular bone mineral content and density (pharmacology)
  - 6 month rat & monkey chronic tox studies:
    - Increases in muscle volume

BMS-986089: Phase 1 Safety

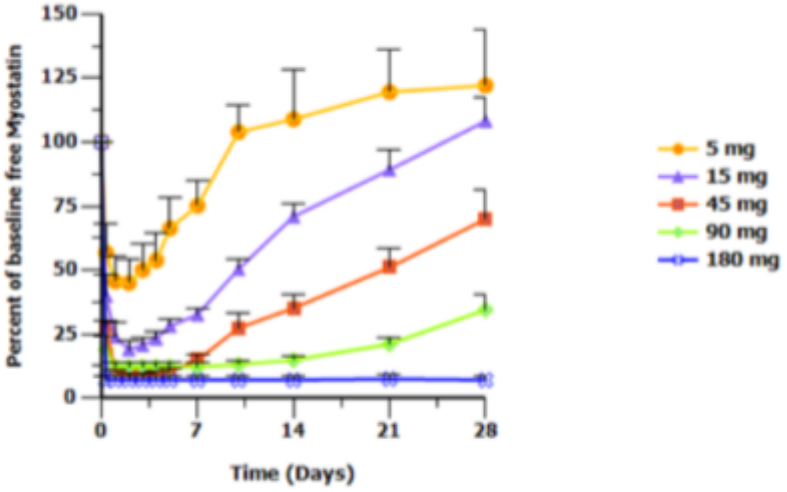
- Single and multiple ascending dose panels in healthy adults have completed
- Preliminary findings:
  - Single and multiple weekly subcutaneous doses of up to 180 mg BMS-986089 appear to be safe and well tolerated
  - Most common adverse effects were mild injection site erythema, rash and injection site reaction
  - Increases in thigh muscle volume (measured using MRI) were observed following multiple dosing

Pharmacokinetics & Target Engagement of BMS-986089 (SAD)

BMS-986089 concentration (PK)

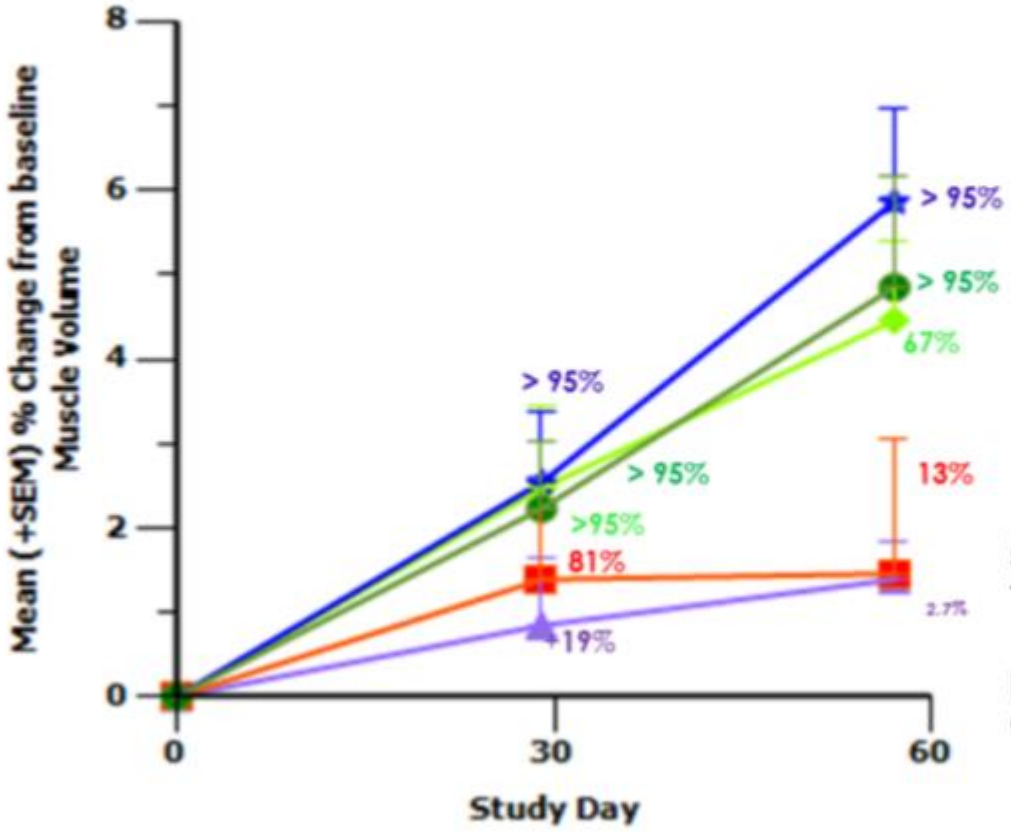


Free myostatin - Percent of baseline



- BMS-986089 has a Tmax of 3-5 days post SC administration.
- Exposure increases were generally dose proportional up to 90 mg and greater than dose proportional at 180 mg
- BMS-986089 binds to and reduces free myostatin in serum.
- Extent and duration of free myostatin suppression increases with dose

BMS-986089 increases muscle volume in healthy volunteers



5 weekly doses; last dose day 28
Time and dose-dependent effects

Embedded values represent
% reduction in free serum myostatin

Increases in Lean Body Mass (measured using DXA imaging) were observed at Study Day 57 in subjects receiving doses of 45 mg/wk or more

Summary of Preliminary Phase I Findings

- Phase I data suggest that BMS-986089 is safe and well tolerated in single and weekly multiple subcutaneous doses of up to 180 mg
- Exposure increased dose proportionally up to 90 mg and greater than dose proportionally above 90 mg
- Extent and duration of free myostatin suppression increased with dose
- Treatment with 5 weekly doses of 45 mg or more of BMS-986089 was associated with increases in thigh muscle volume and total lean body mass in healthy adults

Ongoing: Study of BMS-986089 in boys with Duchenne

- Multi-site, randomized, placebo-controlled, double-blind, ascending weekly subcutaneous dose study to assess safety and tolerability of BMS-986089 in ambulatory boys with Duchenne
- Outpatient 24 week double blind phase (randomized to BMS-986089 or PBO), followed by 48 week open label phase
- Sites in US & Canada
- Travel support is available

Study Objectives

- Primary:
  - Assess safety and tolerability of multiple SC doses of BMS-986089 in boys with Duchenne
- Secondary:
  - Evaluate PK, immunogenicity, free myostatin and myostatin drug complex
  - MRI/MRS measure of thigh muscle fat/lipid fraction

Study Design

- A total of at least 40 ambulatory subjects with Duchenne, age ≥ 5 to < 11 years old (age at randomization)
  - All subjects will receive weekly SC doses of study drug (BMS-986089 or placebo)
- Double Blind Phase includes 24 weeks of dosing
- Upon completing 24 weeks of double blind dosing, all subjects will be eligible to enter the Open Label phase
  - All subjects will receive unblinded BMS-986089 SC doses, weekly, for 48 weeks
- Once subjects complete the OL phase, they may be offered the opportunity to enroll in a separate OL roll-over treatment protocol, if appropriate

Key Criteria

Inclusion

- Diagnosis of Duchenne, confirmed by medical history & genotyping
- Ambulatory boys ages ≥ 5 to < 11 years
- Corticosteroid use for the past 6 months
- 4 stair climb ≤ 8.0 seconds

Exclusion

- EF < 55% on echo
- Cognitive impairment or behavioral issues interfering with ability to complete study procedures
- Treatment with Ataluren or any investigational drug within 3 months or 5 half lives prior to the start of study drug
- Major surgery within 6 weeks of starting study drug

Dosing and Procedures

- Weekly subcutaneous dosing
  - At home dosing is possible after the third dose
- Procedures include:
  - Vital signs, physical exam, ECG, echocardiograms, blood draws
  - Imaging studies
  - Measures of function, including TFTs, 6MWT, NSAA

Further Information

Visit Bristol-Myers Squibb Study Connect Patient and Care Giver Portal to *subscribe* for updates on the DMD clinical study(s)

www.bmsstudyconnect.com/

or

Visit **www.clinicaltrial.gov**

For any additional questions please call or email Bristol-Myers Squibb at:

855-907-3286

Clinical.Trials@bms.com