Givinostat in DMD

PPMD Annual Meeting, June 28th 2019

Dr. Paolo Bettica, VP R&D Italfarmaco

Disclosure and Disclaimer

- Dr. Bettica is a full time employee of Italfarmaco, the manufacturer of Givinostat
- Givinostat (ITF2357) is currently in development for the treatment of DMD and BMD. It is not approved for sale in any country including USA
- This presentation is intended for dissemination and discussion of scientific information only

AGENDA

- Role of Givinostat (ITF2357) in Duchenne Muscular Dystrophy
- Brief review of Givinostat Clinical Data
- Update on Phase 3 study

Role of HDAC in the Pathogenesis of Duchenne Muscular Dystrophy

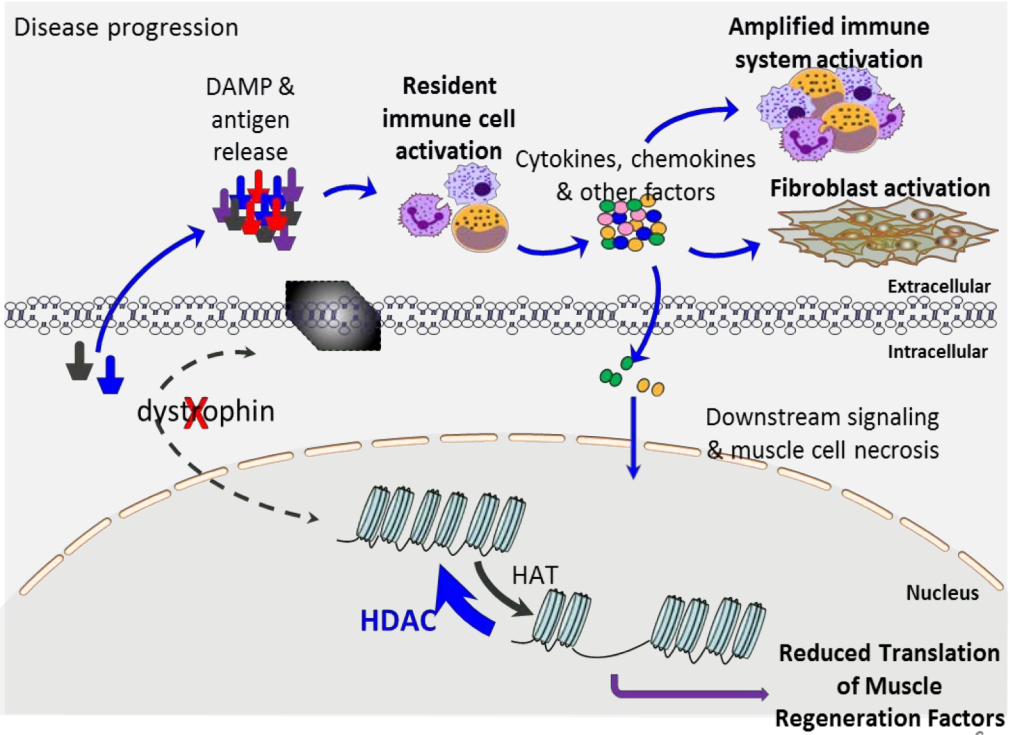
Downstream effects of the lack of dystrophin

Mechanical effects :

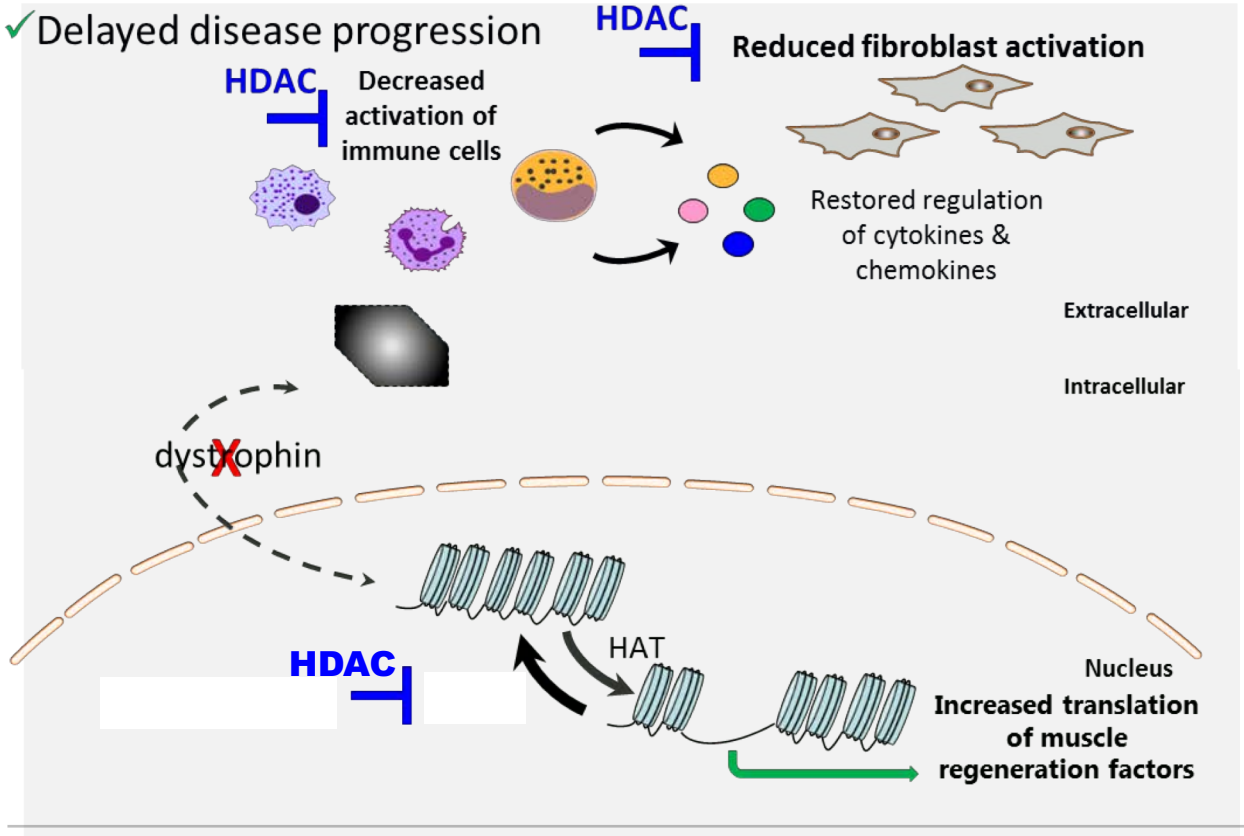
- Increased muscle damage
- Muscle cell membrane instability
- Muscle cell necrosis

Epigenetic effects:

- **Direct:** Lack of DAPC leads to a hyperactive HDAC repressing the translation of muscle regeneration factors
- **Indirect**: Damage-associated molecular pattern (DAMP) release and increased cytokines lead to activation of immune cells and fibroblast, which can be halted by HDAC inhibition



Givinostat Mechanism of Action in DMD Patients



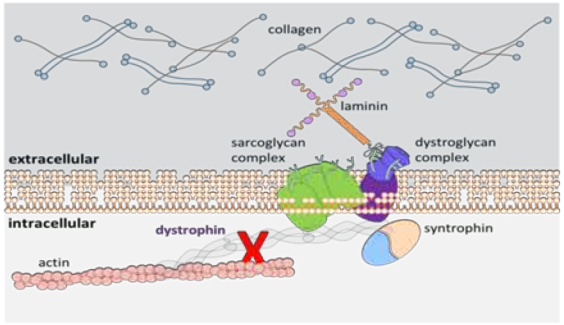
Impact on the epigenetic effects of the lack of dystrophin

HDAC inhibition:

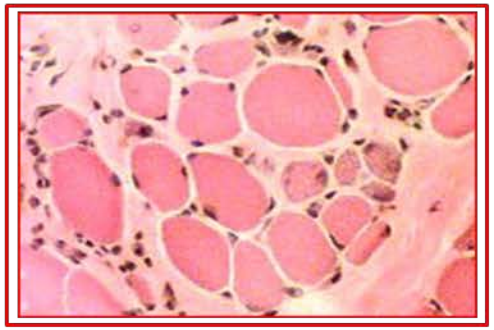
- ✓ Increased translation of muscle regeneration factors with an increase in muscle regeneration
- ✓ Reduced activation of immune cells with a reduction in pro-inflammatory cytokine release
- ✓ Reduced fibroblast activation with a reduction in fibrosis

Restoring the Balance in DMD Patients with Givinostat

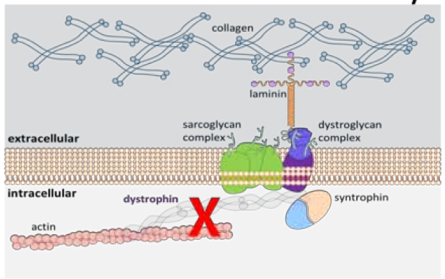
Duchenne Muscular Dystrophy Muscle



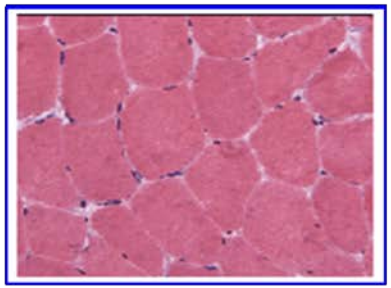
- Tissue damage
- Myofibril necrosis
- Chronic inflammation
- Aberrant adipocyte formation
- Reduced Muscle Fiber Regeneration



Duchenne Muscular Dystrophy Muscle + Givinostat



- Reduced Tissue damage
- Reduced Myofibril necrosis
- Reduced Chronic inflammation
- Reduced Aberrant adipocyte formation
- Increased Muscle Fiber Regeneration



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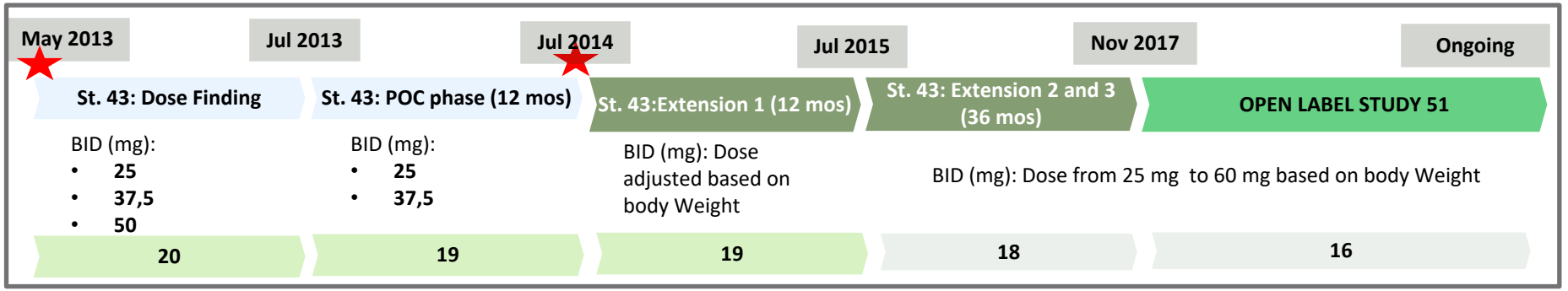
Phase II Study 43 and OLE Study 51: Trial design and patient disposition

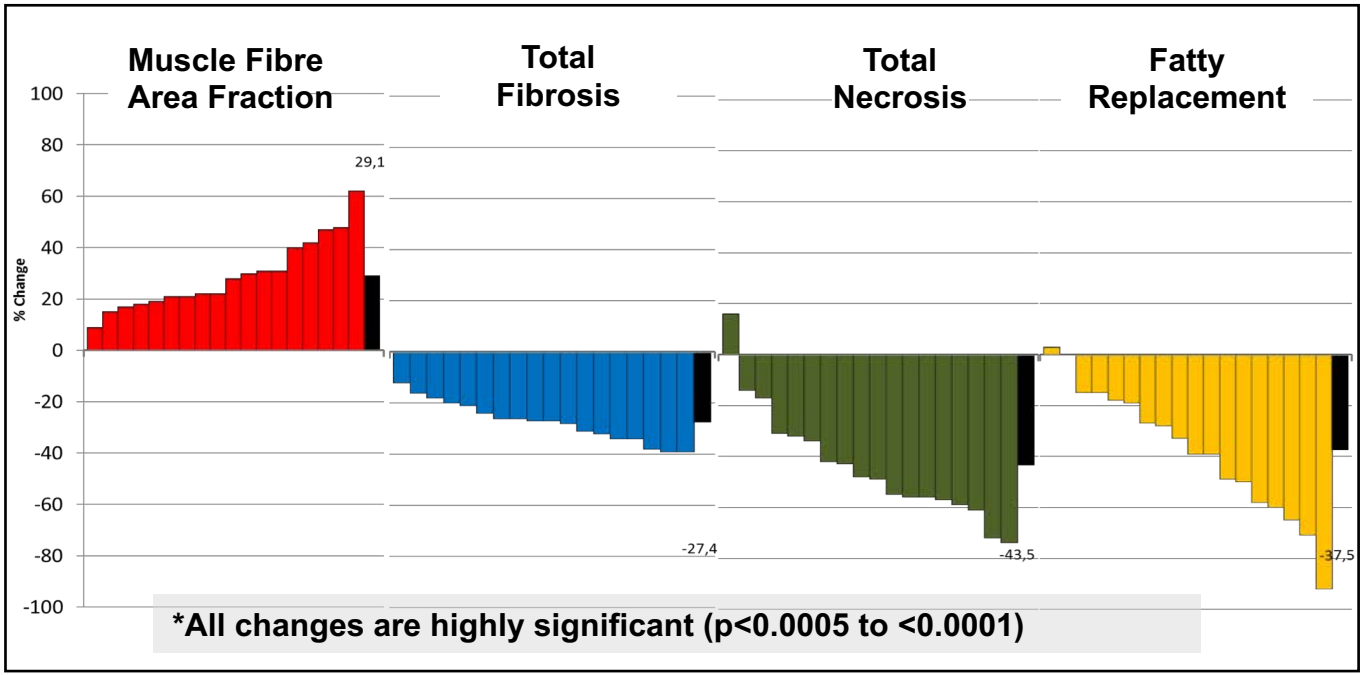
Study 43 enrolled 20 ambulant DMD boys aged 7-11 yrs at baseline and on stable steroids. 18 of them completed Study 43 and entered study 51. 16 boys are currently still on treatment.



	Baseline	Month 12	Month 24	Month 36	Month 48	Month 52	Month 64
	Mean (range)	Mean (range)	Mean (range)	Mean (range)	Mean (range)	Mean (range)	Mean (range)
Age	8.6 (7-10.7)	9.9 (8.2-11.9)	10.9 (9.2-12.9)	12 (10.2-13.9)	13 (11.2-14.9)	13.3 (11.6-15.2)	14.4 (12.6-16.2)
N	19	19	19	18	18	18	16

Phase II Study 43: Histological results

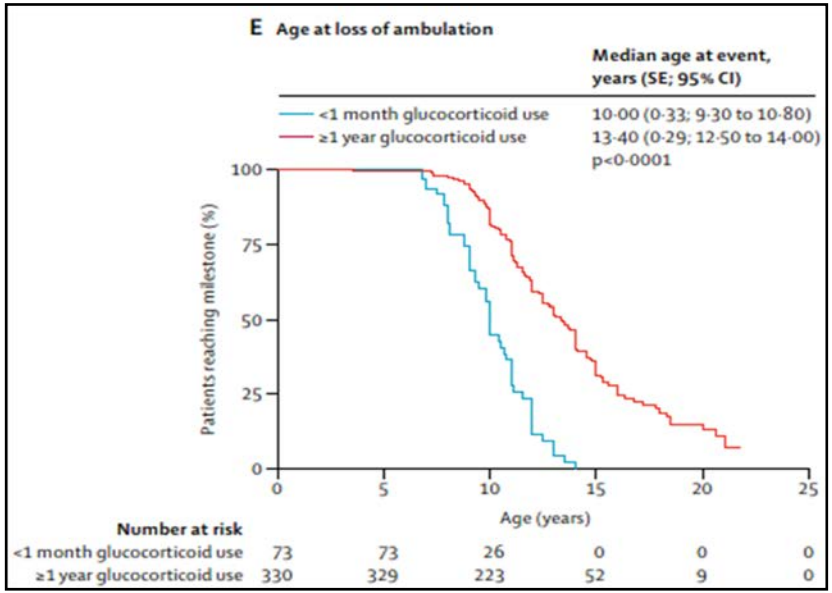
Givinostat histological results on Muscle Fibres Area Fraction (MFAF), fibrosis, necrosis and fatty replacement are consistent across all children



Age at Loss of Ambulation: Natural History from CINRG

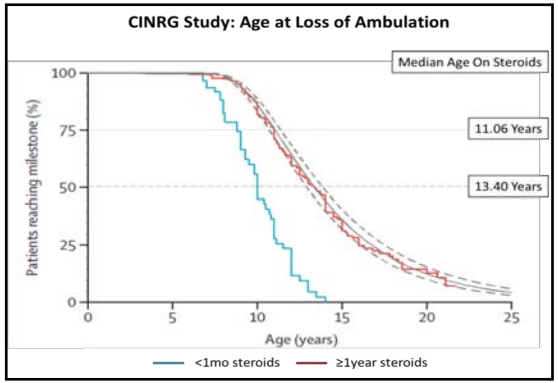
Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study

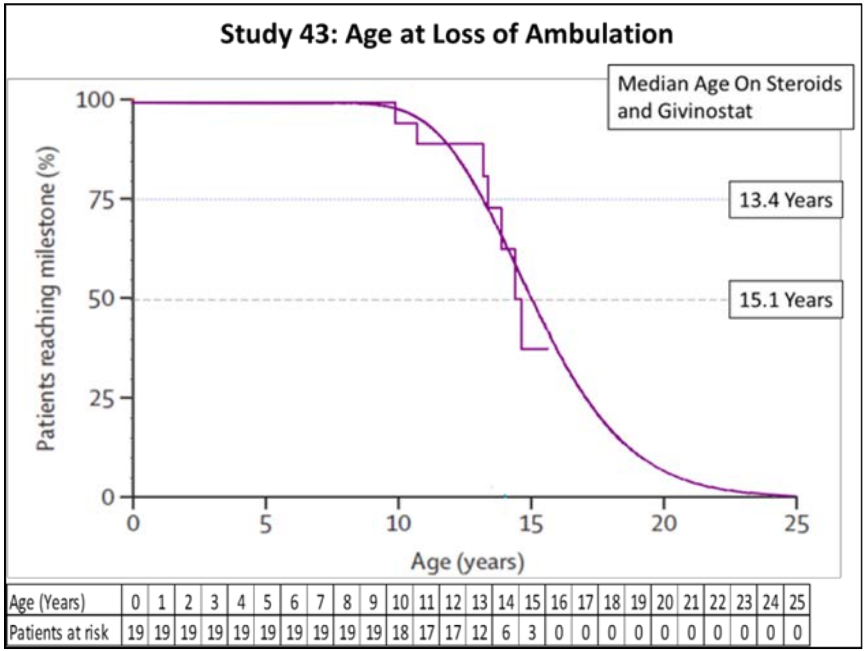
*Craig M McDonald, Erik K Henricson, Richard T Abresch, Tina Duong, Nanette C Joyce, Fengming Hu, Paula R Clemens, Eric P Hoffman, Avital Cnaan, Heather Gordish-Dressman, and the CINRG Investigators**



Study 43-51: Givinostat Effect on Loss of Ambulation

Contrasted with the natural history published results (CINRG study[1]) study 43-51 results suggest that the addition of Givinostat to steroid treatment delays disease progression





Age (Years)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Patients at risk	19	19	19	19	19	19	19	19	19	19	18	17	17	12	6	3	0	0	0	0	0	0	0	0	0	0

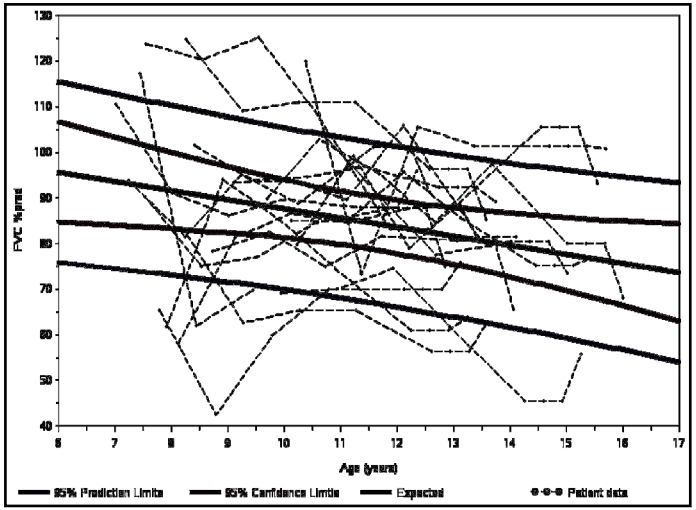
[1] *McDonald et al. 2018*

Study 43-51 : Givinostat effects on Pulmonary Function

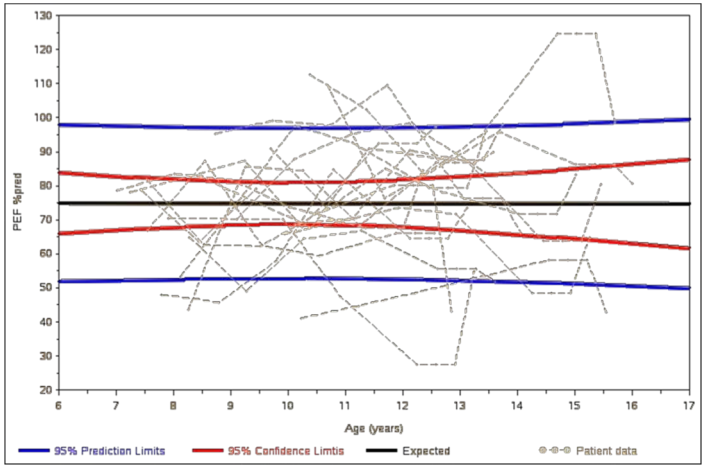
A 4 to 6% yearly rate[1, 2, 3] of decline in FVC% Predicted and PEF% Predicted has been shown in natural history studies in a patient population comparable to that of Study 43-51.

Givinostat treatment for 5.4 years leads to a delay in the decline of the respiratory parameters (Forced Vital Capacity, FVC & Peak Expiratory Flow, PEF)

FVC% Predicted: 2.0% yearly decline



PEF% Predicted: No decline



[1] Mayer et al. Paediatr Pulmonol 2015; [2] Henricson et al. Muscle Nerve, 2013; Abresch et al. Neuromuscul Disord, 2013; [3] Kinane et al. Journal of Neuromuscular Diseases 2018

Study 43: Safety Data

- ✓ *8 subjects (40%) experienced at least one Serious Adverse Event:*
  - *Only 2 SAEs were related and the events were "platelets count decreased"*
- ✓ *All subjects experienced at least one AEs; most of the AEs were mild or moderate in intensity, 11 events were severe; only one subject discontinued from the study due to SAE (i.e "platelets count decreased") during part 1 of the study at 50 mg BID*
- ✓ *The most common Related Adverse Events (i.e. at least 4 subjects) were:*

	All AEs N (%)	Drug Related N (%)
Diarrhoea	**15 (75)**	**15 (75)**
Platelet count decreased	**14 (70)**	**14 (70)**
Abdominal pain	**11 (55)**	**9 (45)**
Decreased appetite	**7 (35)**	**7 (35)**
Vomiting	**8 (40)**	**5 (25)**
White blood cell count decreased	**4 (20)**	**4 (20)**

Givinostat Study 43-51: Data analysis conclusions

- ✓ *Givinostat's open-label phase 2 study (Study 43) met its primary endpoint (statistically significant histologic effects)*
- ✓ *Long term results vs natural history data suggest a delay of the disease milestones*
- ✓ *Givinostat was safe at the doses used*

Stage / Study		Result
Histological Effects		✓
Macroscopic level: MRI data		✓
Efficacy on function	Effect on Ambulation	✓
	Respiratory and Upper Limb function data	✓

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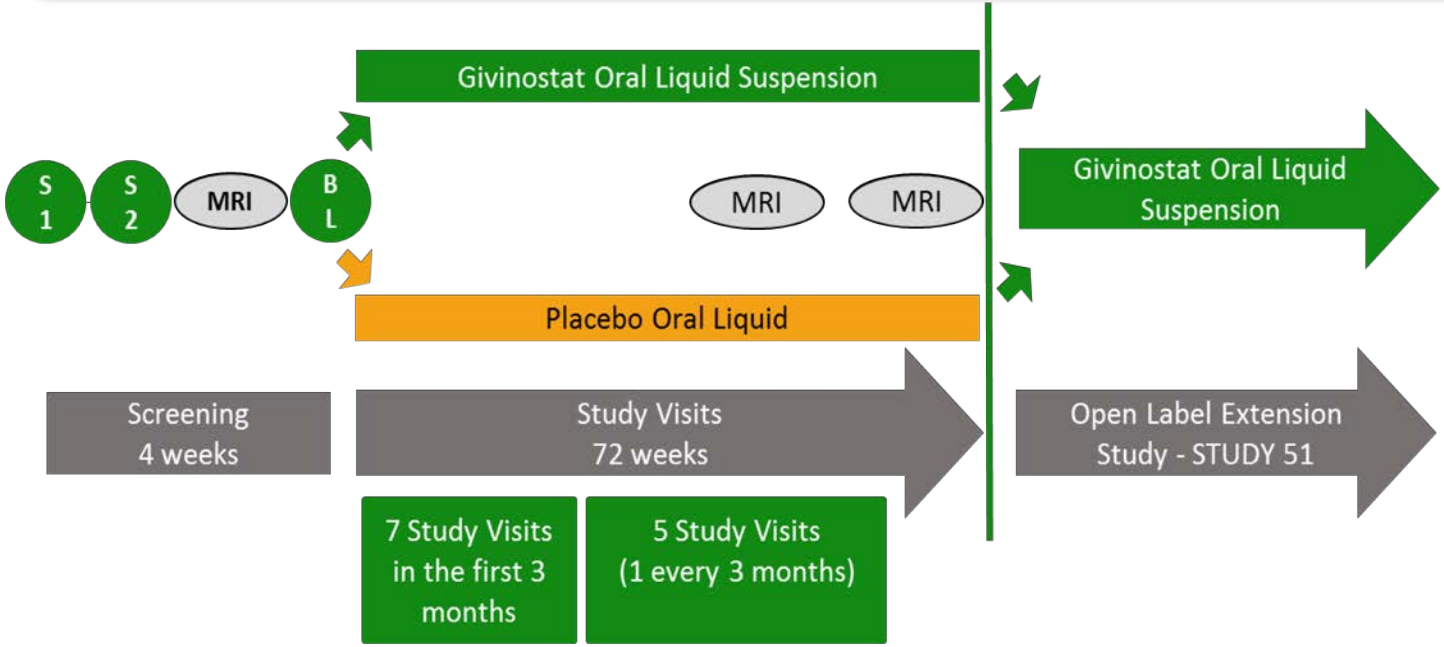
Phase 3 Study in Duchenne Ambulant Boys

Study Objectives

to demonstrate that Givinostat preserves muscle mass and slows down disease progression evaluating:

- the functional effects by function tests
- the morphological effects by MRI



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What Happens at Study Visits?

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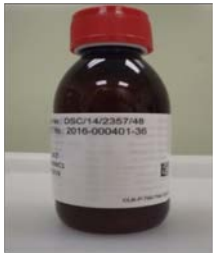
- **Informed Consent Paperwork**
- Attend the clinical visits, in total of **15 visits** (every 3 months):
  - Blood draw more frequently during the first 3 months:
    - first month: weekly
    - second month: every 2 weeks
    - from the third month: every 3 months
  - Surveys (baseline, at 12 and 18 months) and Diaries (every visit)
  - Muscle tests every 3 months (6MWT, NSAA, 4SC, QMT)
  - Pulmonary Function test baseline, at 12 and 18 months
  - Thigh muscle **MRI**: <u>baseline, at 12 and 18 months</u>
- Upon successful completion of the study, participants, **regardless** the ability to walk, will have the opportunity to enter into long term safety study and they will ALL receive the drug



Givinostat or Placebo
Liquid Oral Suspension
Twice a day after food

Amended Protocol: New Criteria

Key Inclusion Criteria:

- Can walk (no criteria on distance or velocity)
- Be age 6 or older
- Have genetic diagnosis of DMD
- Can climb 4 stairs in ≤ 8 seconds
- Can get up off the floor in ≥ 3 and <10 seconds
- Are taking steroids at stable dosage for at least 6 months
- Can do an MRI
- Can do stair test consistently (the results of 2 tests must be within ±1 second of each other)

Key Exclusion Criteria:

- Take other investigational drugs, idebenone, exon skipping, or premature stop codon readthrough drugs.
- Take other drugs that affect strength or muscle function (e.g. growth hormone)
- Have ankle contractures (i.e. fixed loss of more than 10 degrees of plantar flexion from plantigrade)
- Will have surgery soon
- Are not healthy enough for the study (e.g. ejection fraction <50%; uncontrolled neurological diseases)

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Trial Support Program

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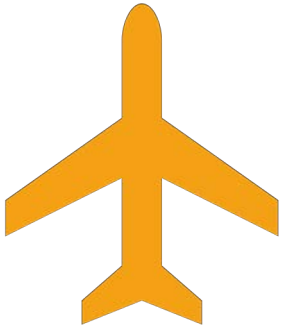
- Home nursing visits available at Week 2, 3, 8 and any unscheduled visits, if necessary



- Central travel and reimbursement support available for all participants families

- Open label extension study open to everyone who finishes the trial.

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Clinical Sites

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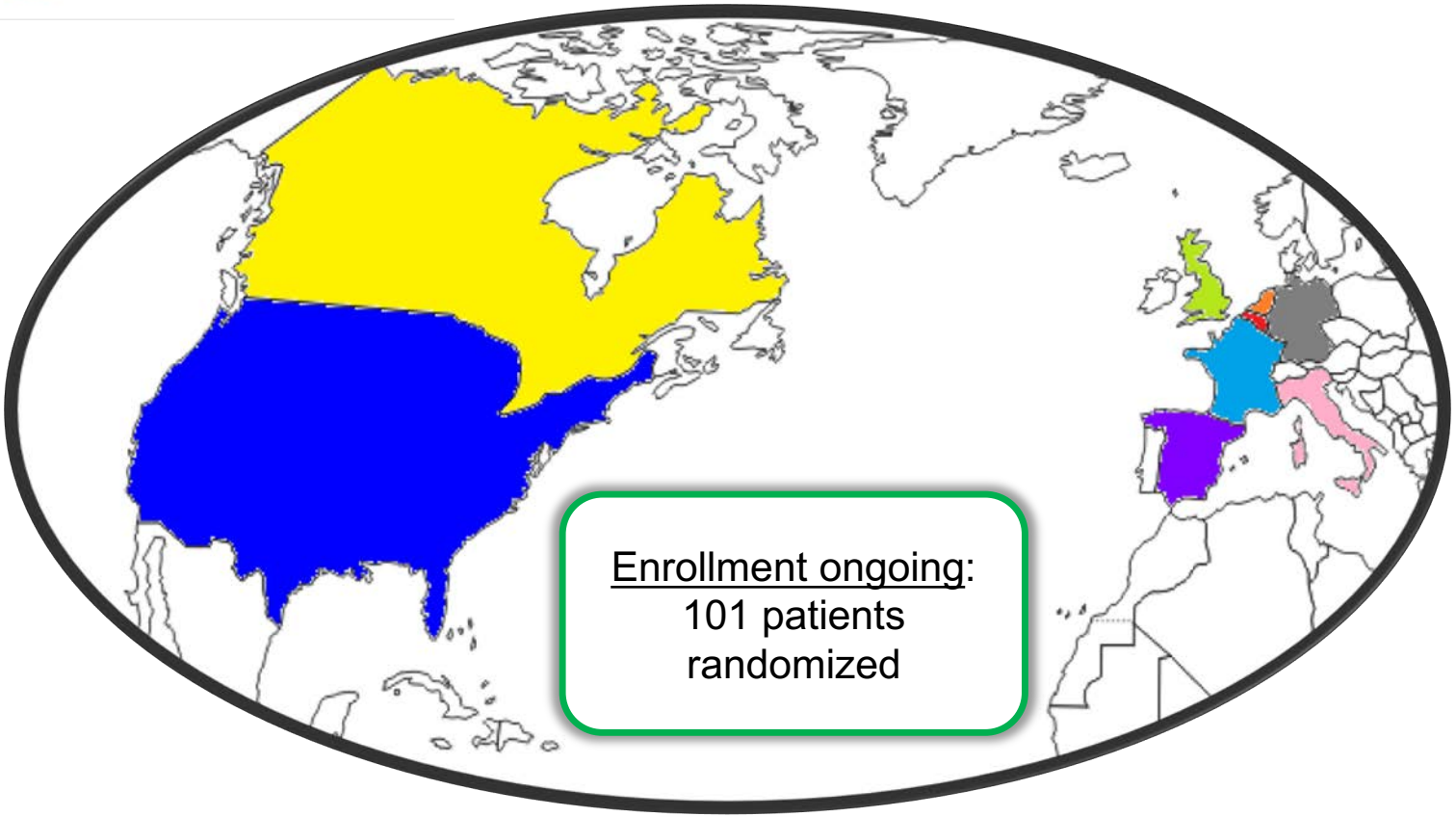

Enrollment ongoing:
101 patients
randomized

Acknowledgment

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Cure Duchenne Cares

EndoStem

Parent Project Muscular Dystrophy

JOIN THE FIGHT. END DUCHENNE.

DUCHENNE DATA FOUNDATION

IMAGING DMD

ON TOP OF THE FIGHT FOR A CURE

Jett FOUNDATION

Asociación Duchenne Parent Project España

contra la distrofia muscular de Duchenne y Becker

צעדים קטנים

עמותה למען ילדים חולי דושן ובקר (ע"ר)

FONDAZIONE Telethon

- Patients and Families
- Clinical Sites
- Patients' associations

Duchenne Parent Project onlus

TREAT-NMD Neuromuscular Network

ACTION DUCHENNE

DUCHENNE UK

Learn more information on https://clinicaltrials.gov/ Study Number: NCT02851797

or

Ana Christensen, MPH
Patient Science Liaison for Italfarmaco
Email: patientadvocacy@italfarmaco.com (412) 593-4389