Givinostat in DMD

PPMD Annual Meeting, June 29th 2018

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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 - Phase 2 study
- Phase 3 study

Role of HDAC in the Pathogenesis of Duchenne Muscular Dystrophy

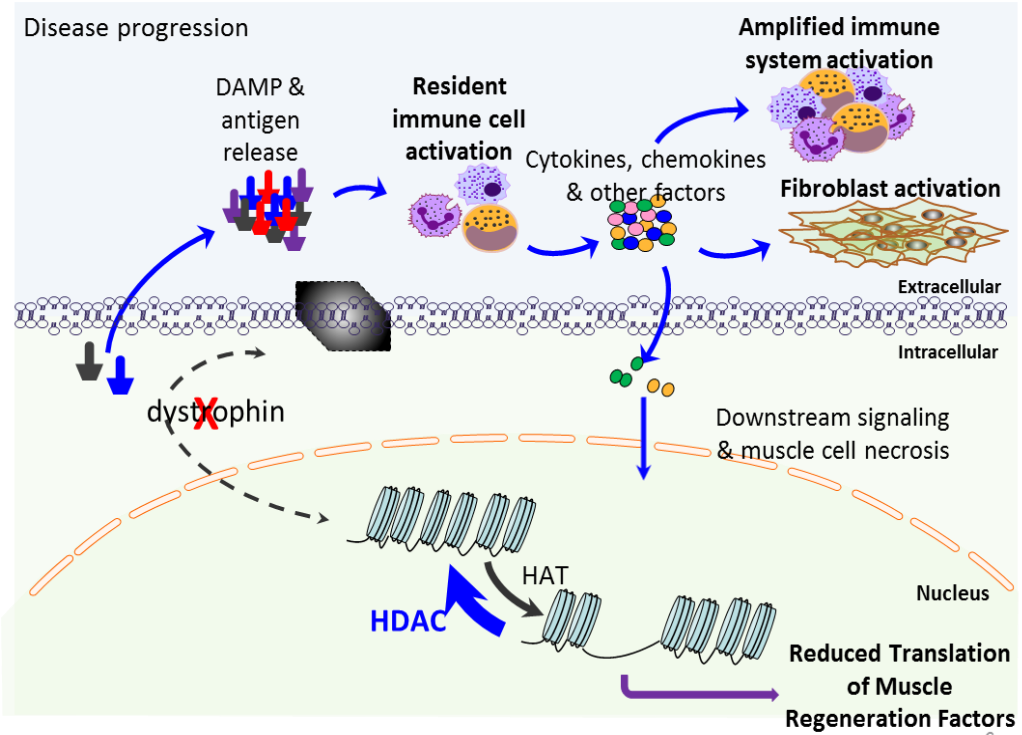
Downstream effects of the lack of dystrophin

Mechanical effects :

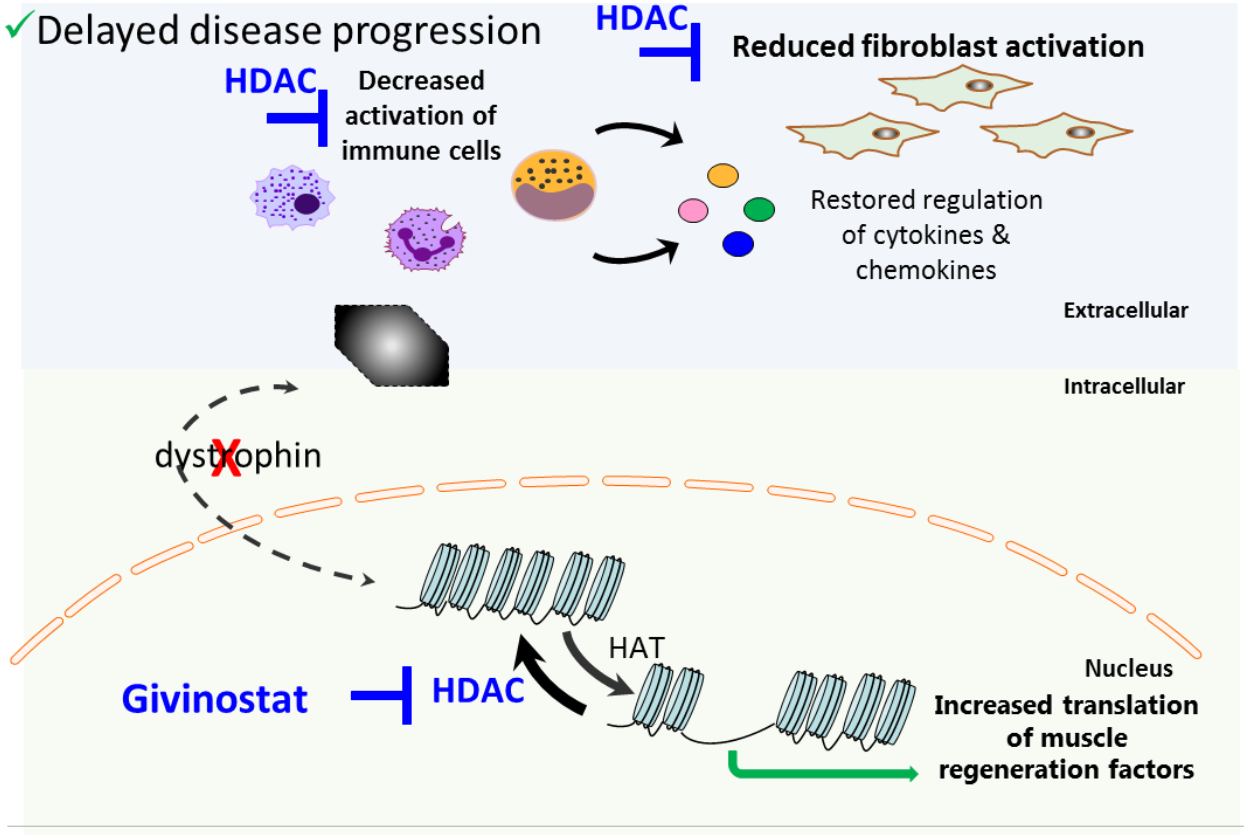
- Increased muscle damage
- Muscle cell membrane instability
- Muscle cell necrosis

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



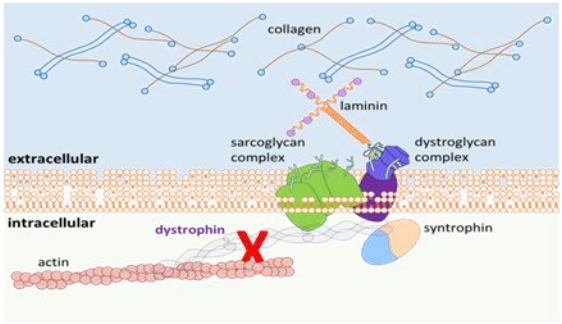
Impact on the epigenetic effects of the lack of dystrophin

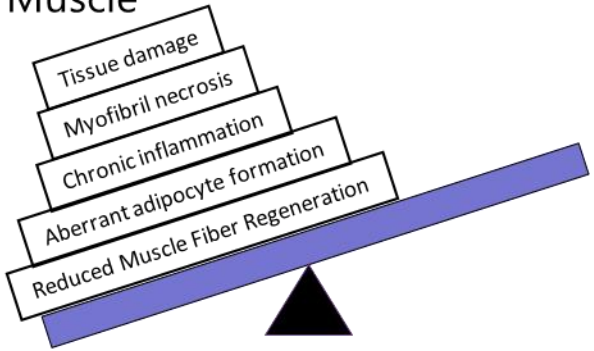
HDAC inhibition:

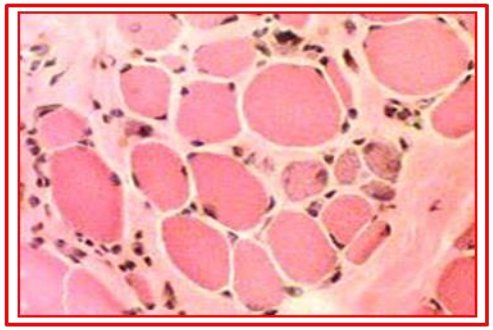
- ✓ Increased translation of muscle regeneration factors with an increase in muscle regeneration
- ✓ Reduced activation of immune cells with a reduction in pro-inflammatory cytokine release
- ✓ Reduced fibroblast activation with a reduction in fibrosis

Restoring the Balance in DMD Patients with Givinostat

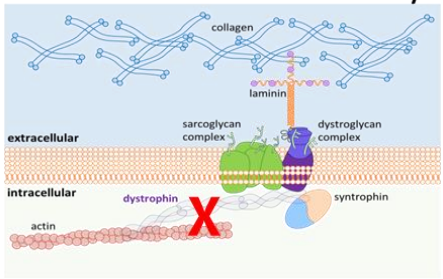
Duchenne Muscular Dystrophy Muscle

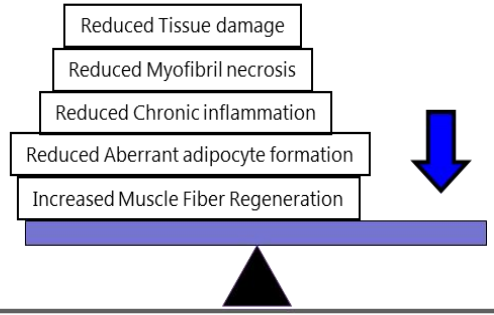


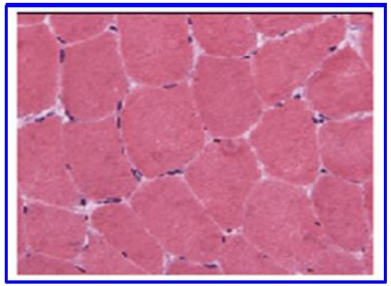




Duchenne Muscular Dystrophy Muscle + Givinostat







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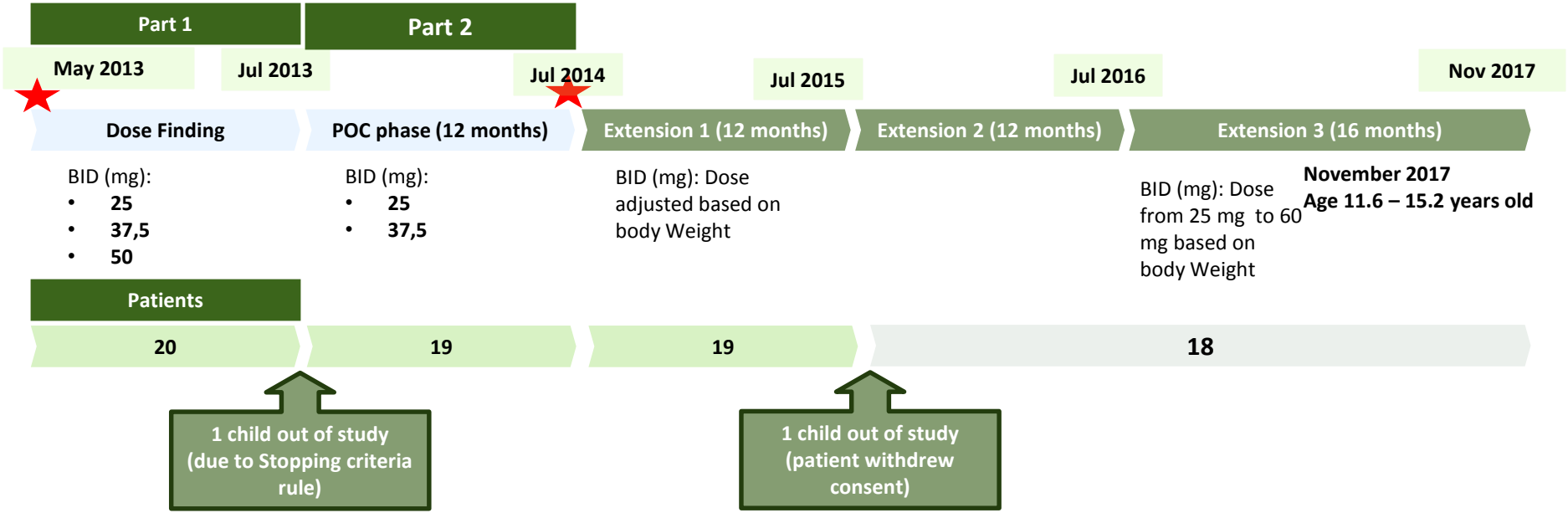
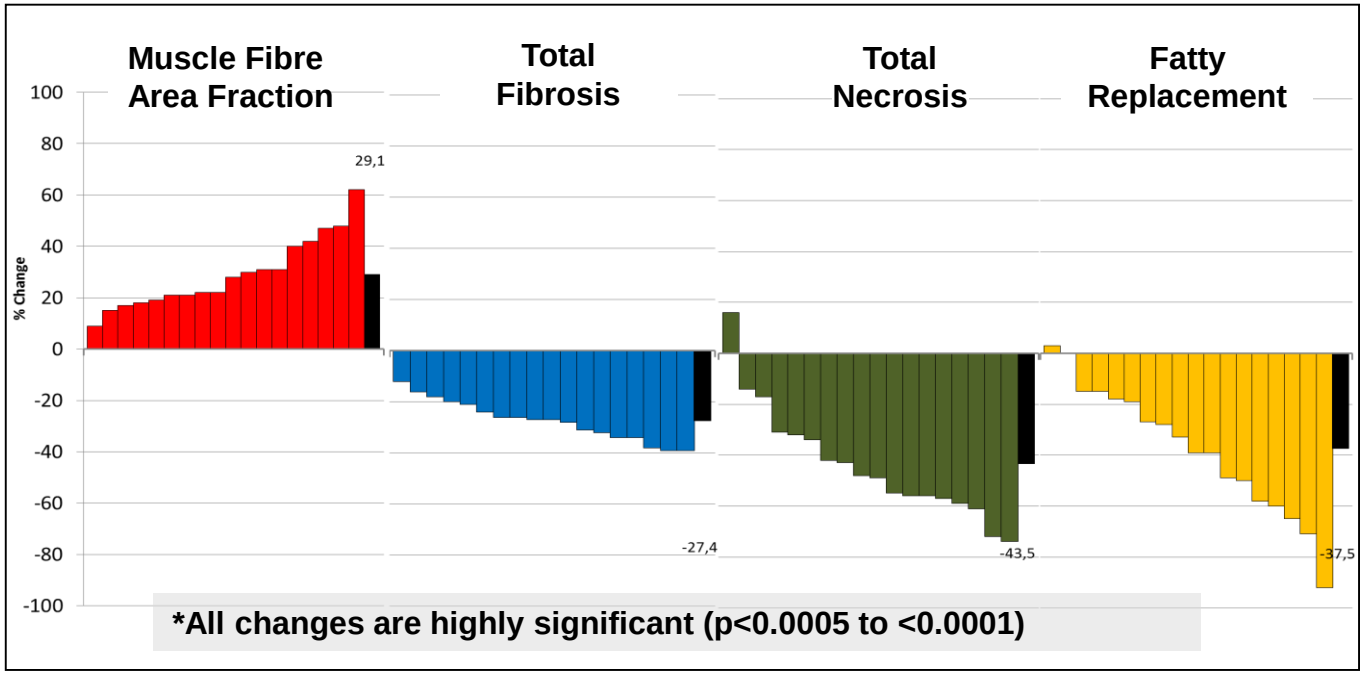
Phase II Study 43: Trial design and patient disposition

Open label phase 2 study: 20 enrolled DMD ambulant boys from 7 to <11 years old, in stable steroids treatment. Boys who completed the study treatment (month 52): 18



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



Phase II Study 43: Givinostat Effect on Ambulation Milestones After 4.4 years

As boys are now in the 5th year of treatment we can evaluate the effect of Givinostat on Disease Milestones, such as Time to Rise >10 seconds and Loss of Ambulation

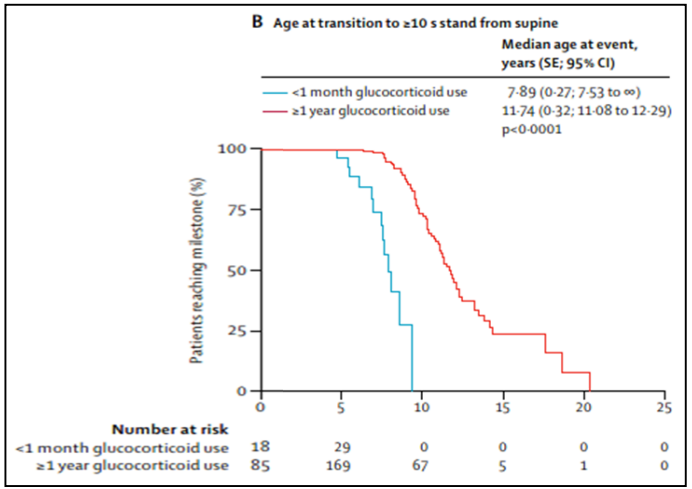
Results in study 43 can be contrasted with recently published CINRG Results (McDonald et al., 2018)

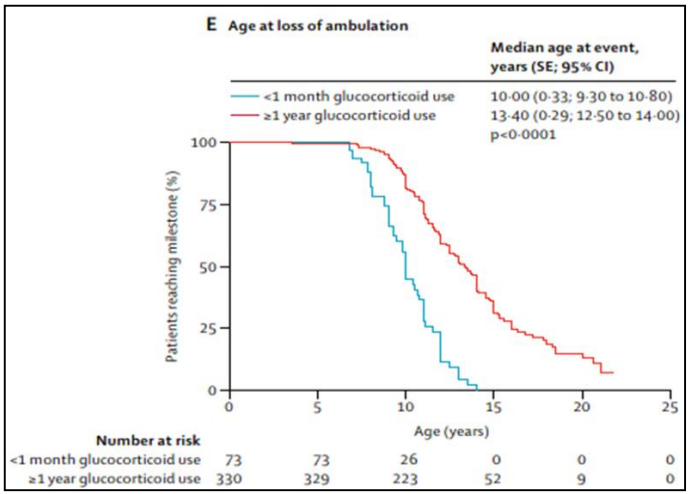
	Baseline	Month 12	Month 24	Month 36	Month 48	Month 52
	Mean (range)	Mean (range)	Mean (range)	Mean (range)	Mean (range)	Mean (range)
Age	8.6 (7-10.7)	9.9 (8.2-11.9)	10.9 (9.2-12.9)	12 (10.2-13.9)	13 (11.2-14.9)	13.3 (11.6-15.2)
N	19	19	19	18	18	18

CINRG Disease Milestone Analysis: Population

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

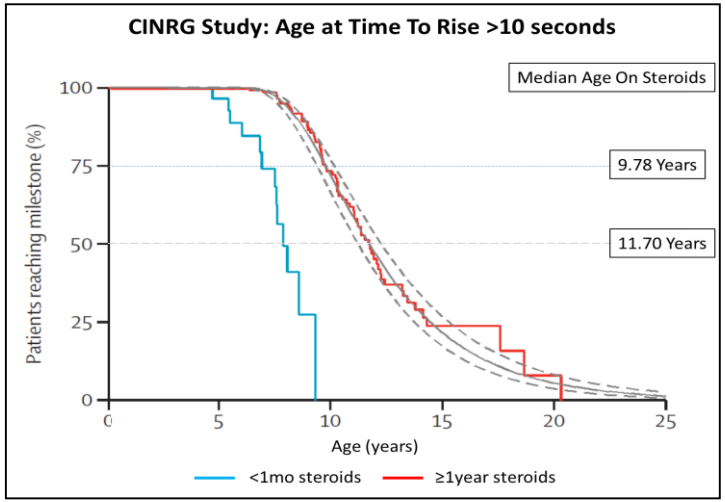
*Craig M McDonald, Erik K Henricson, Richard T Abresch, Tina Duong, Nanette C Joyce, Fengming Hu, Paula R Clemens, Eric P Hoffman, Avital Cnaan, Heather Gordish-Dressman, and the CINRG Investigators**

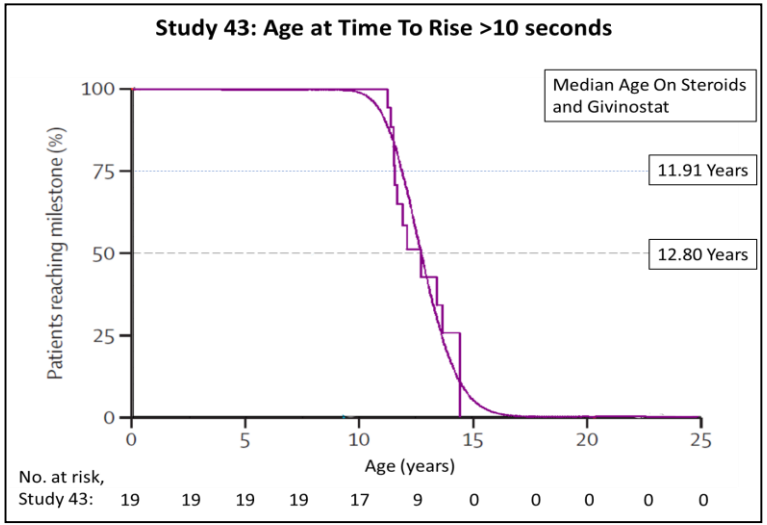




Phase II Study 43: Givinostat Effect on Time To Rise >10 Seconds

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

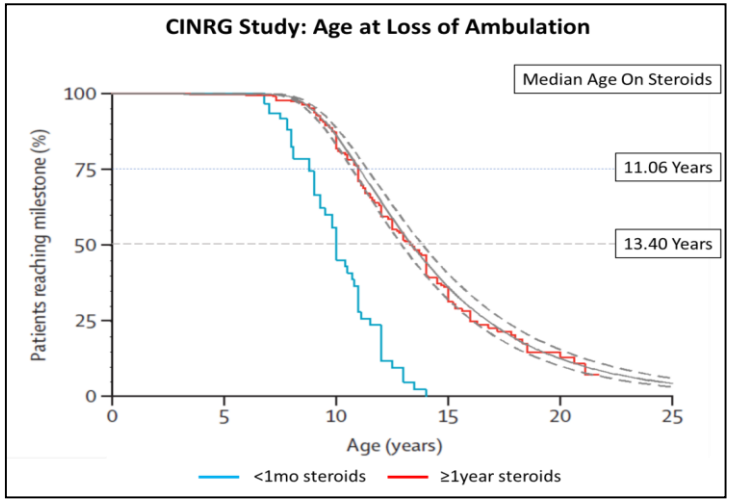


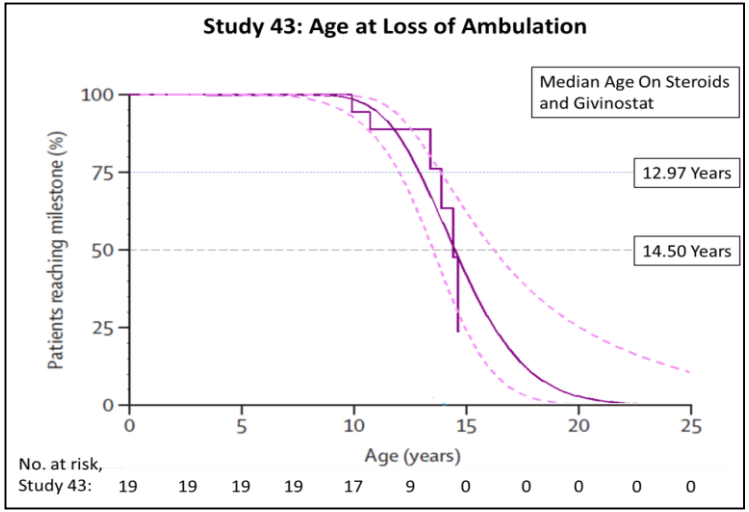


[1] *McDonald et al. 2018*

Phase II Study 43: Givinostat Effect on Loss of Ambulation

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



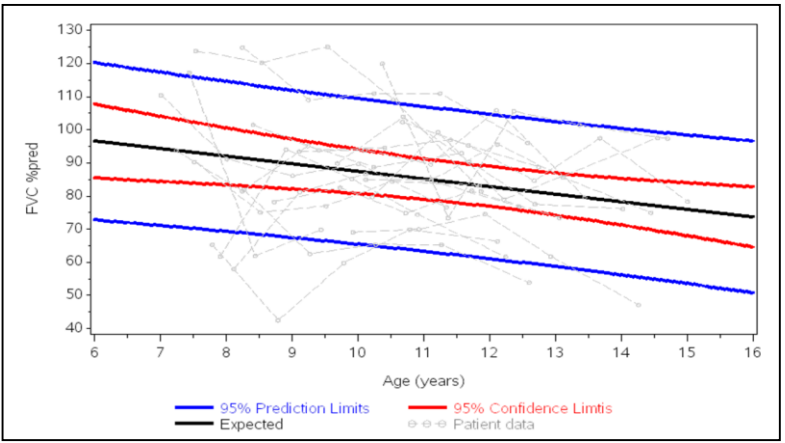


[1] *McDonald et al. 2018*

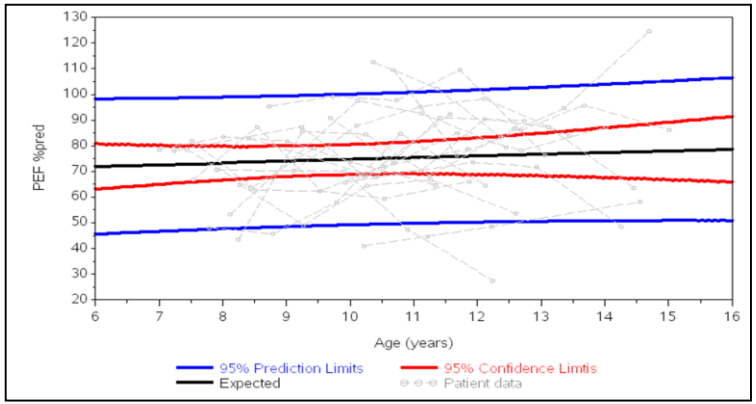
Phase II Study 43: Pulmonary Function

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.
Givinostat treatment for 4.4 years leads to a delay in the decline of the respiratory parameters (Forced Vital Capacity, FVC & Peak Expiratory Flow, PEF)

FVC% Predicted: 2.3% 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

Phase II 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)**

Phase II Study 43: Data analysis conclusions

- ✓ *Givinostat's open-label phase 2 study 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*
- ✓ *Phase 2 results strongly support the execution of a larger phase 3 study to further explore Givinostat's efficacy in Duchenne*

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

epidys
EPIGENETIC RESCUE OF DYSTROPHIN DYSFUNCTION

ITALFARMACO

Study Objectives

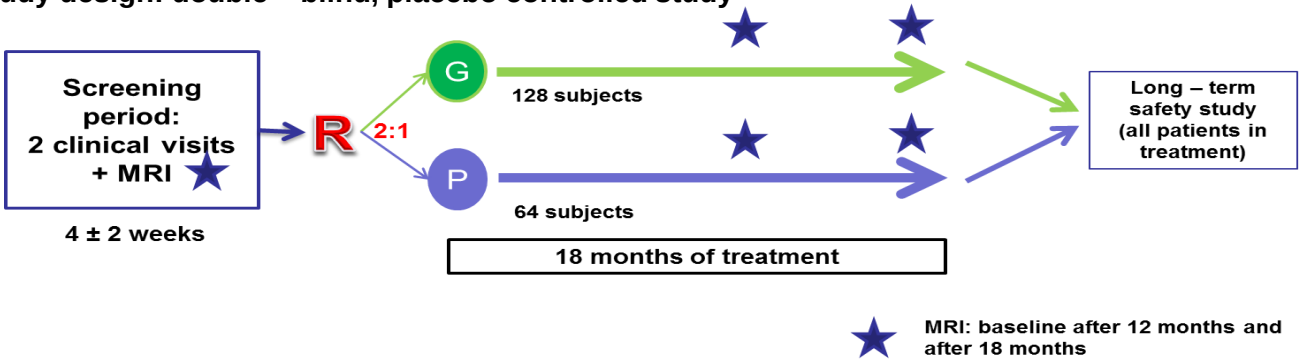
to demonstrate that Givinostat preserves muscle mass and slows down disease progression evaluating:

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

Inclusion/exclusion criteria

- No genetic mutation restriction
- ≥ 6 years old
- on stable corticosteroid for at least 6 months
- able to perform:
  - The 4 stairs climb test in ≤ 8 sec
  - The time to rise test in < 10 sec
- No contraindication to perform MRI (e.g., claustrophobia, metal implants, or seizure disorder)

Study design: double – blind, placebo controlled study



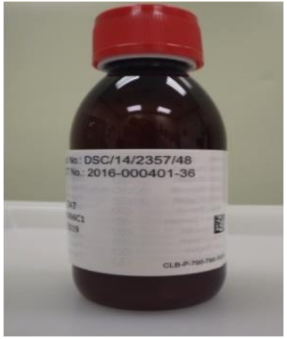
What does participant entail?

- **Sign Informed Consent**
- 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

in some visits a nurse will perform the blood draw at participant's home (Illingworth Research Group)

  - Muscle tests every 3 months
  - Pulmonary Function test baseline, at 12 and 18 months
  - Thigh muscle **MRI**: <u>baseline, at 12 and 18 months</u>

What does participant entail?



- **Take Givinostat/Placebo Oral suspension** twice daily in fed state: after breakfast and after about 12 hour e.g. after dinner or light snack before going to bed at 7 or 8 pm

- Reasonable expenses related to clinical visits will be reimbursed

Family support: family travel planning and /or reimbursement

patient primary
part of the mdgroup

- Upon successful completion of the study, participants will have the opportunity to enter into long term safety study and they will ALL receive the drug

epidys
EPIGENETIC RESCUE OF DYSTROPHIN DYSFUNCTION

Clinical Sites

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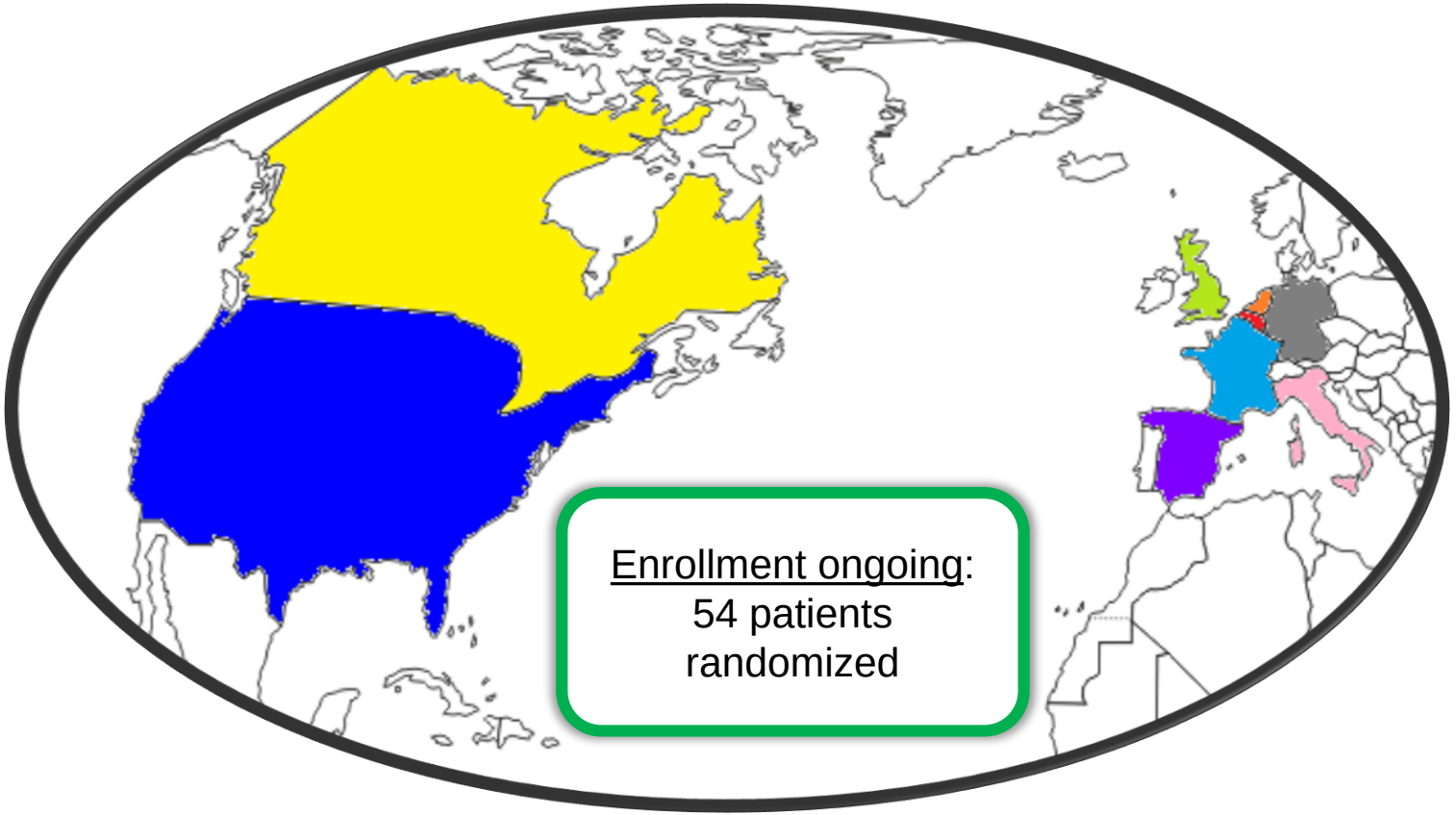

Enrollment ongoing:
54 patients
randomized

Acknowledgment

ITALFARMACO

EndoStem

TREAT-NMD
Neuromuscular Network

Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

IMAGING DMD
ON TOP OF THE FIGHT FOR A CURE

Asociación Duchenne Parent Project España
contra la distrofia muscular de Duchenne y Becker

- Patients and Families
- Clinical Sites
- Patients' associations

Duchenne Parent Project onlus

צעדים קטנים
עמותה למען ילדים חולי דושן ובקר (ע"ר)

FONDAZIONE Telethon

For further information https://clinicaltrials.gov/ using the Identification Number: NCT02851797 for Duchenne
Or email to patientadvocacy@italfarmaco.com