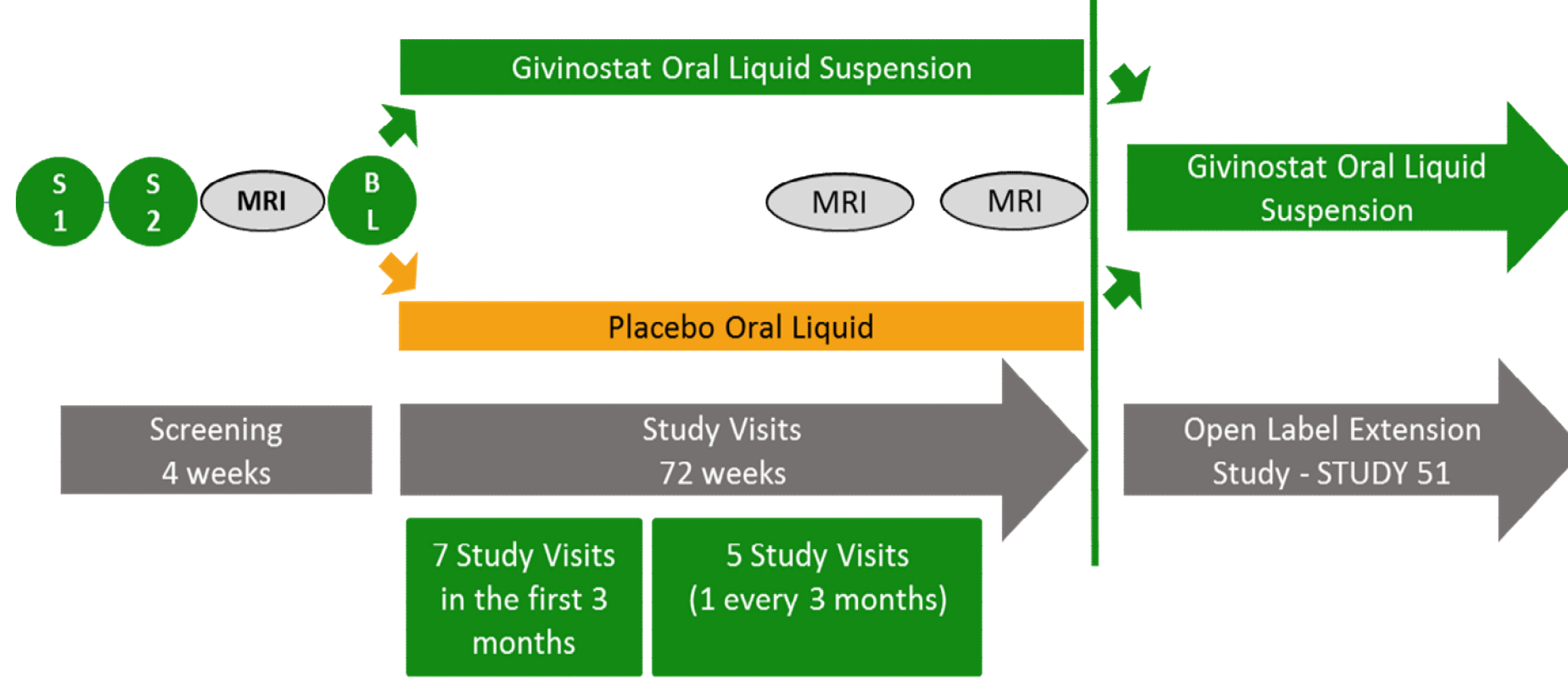


## PHASE 3 TRIAL



Phase 3, multicentre, double blind, placebo controlled (2:1) study in 242 patients to demonstrate that Givinostat oral suspension preserves muscle mass and slows down disease progression. The study is ongoing in USA, Canada and European countries.



### What does participant entail?:

- must be ambulant DMD boys from 6 years of age,
- on stable corticosteroid for at least 6 months prior to start the treatment,
- able to perform the 4 stairs climb in no more than 8 seconds and time to stand up in  $\geq 3$  and less than 10 seconds,
- do the MRI scan

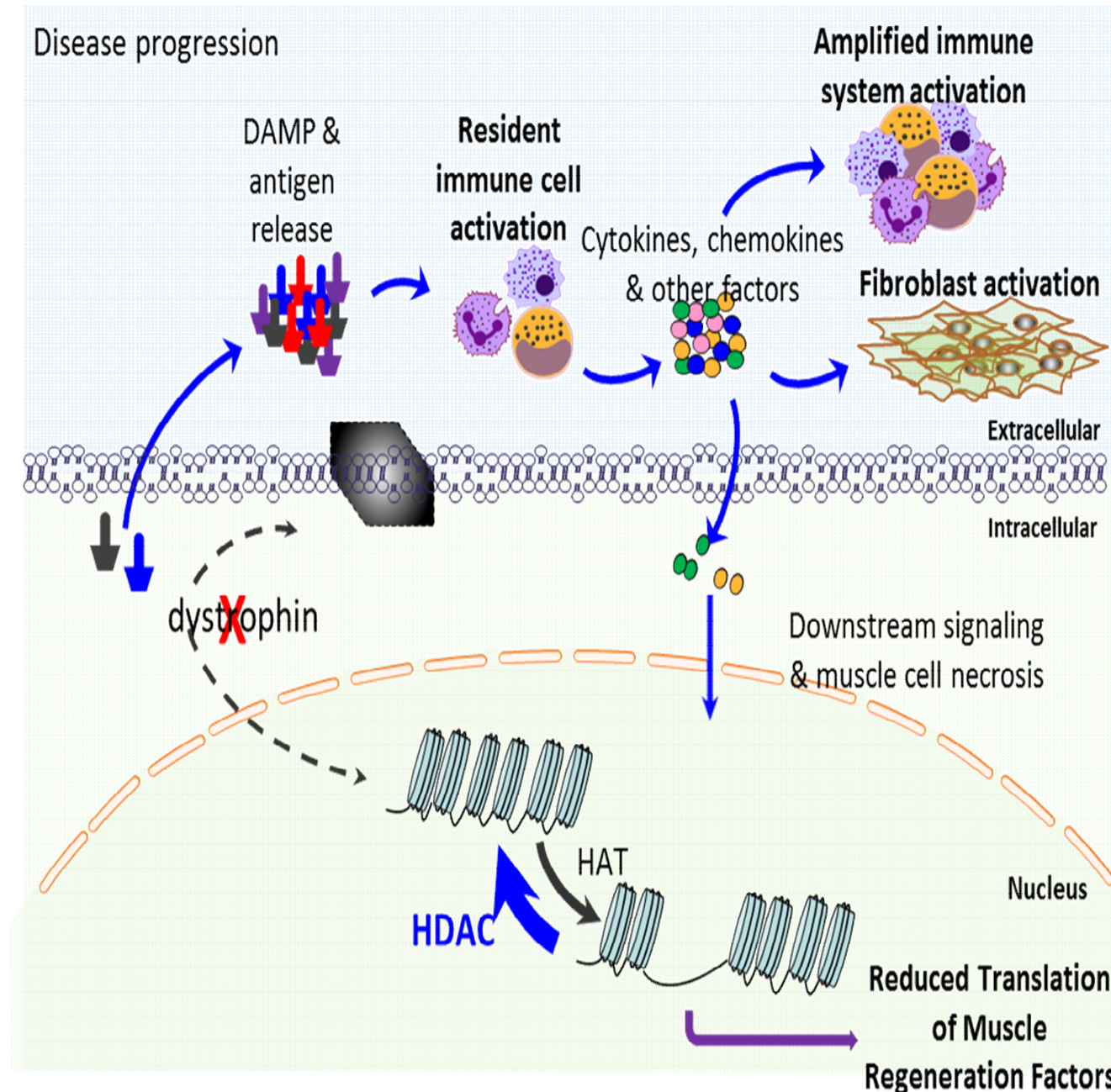
### What happens at study visits?

- Informed Consent Paperwork
- A 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: baseline, at 12 and 18 months
- 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 Mechanism of Action in Duchenne

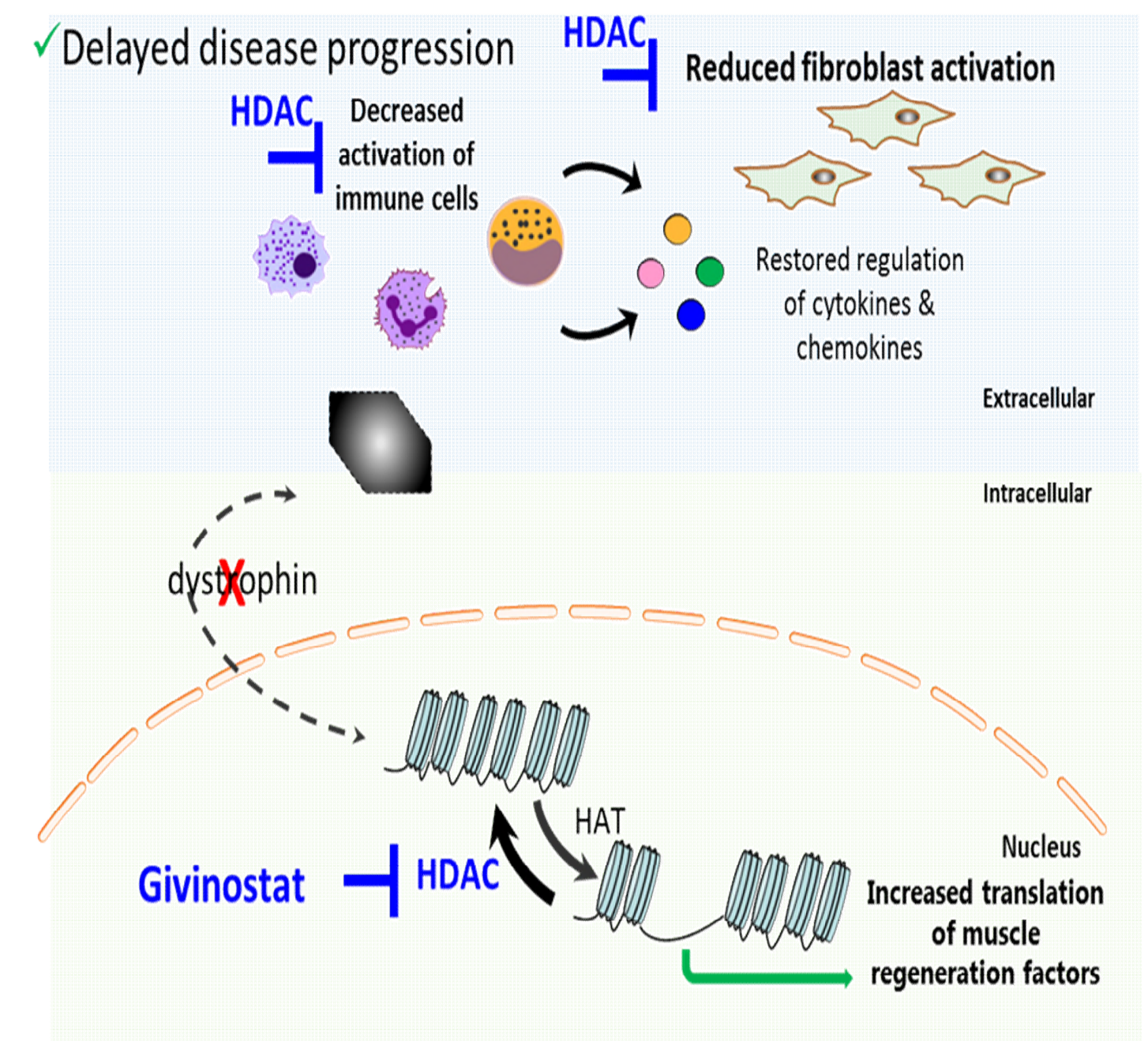
### Downstream effects of the lack of dystrophin

- 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



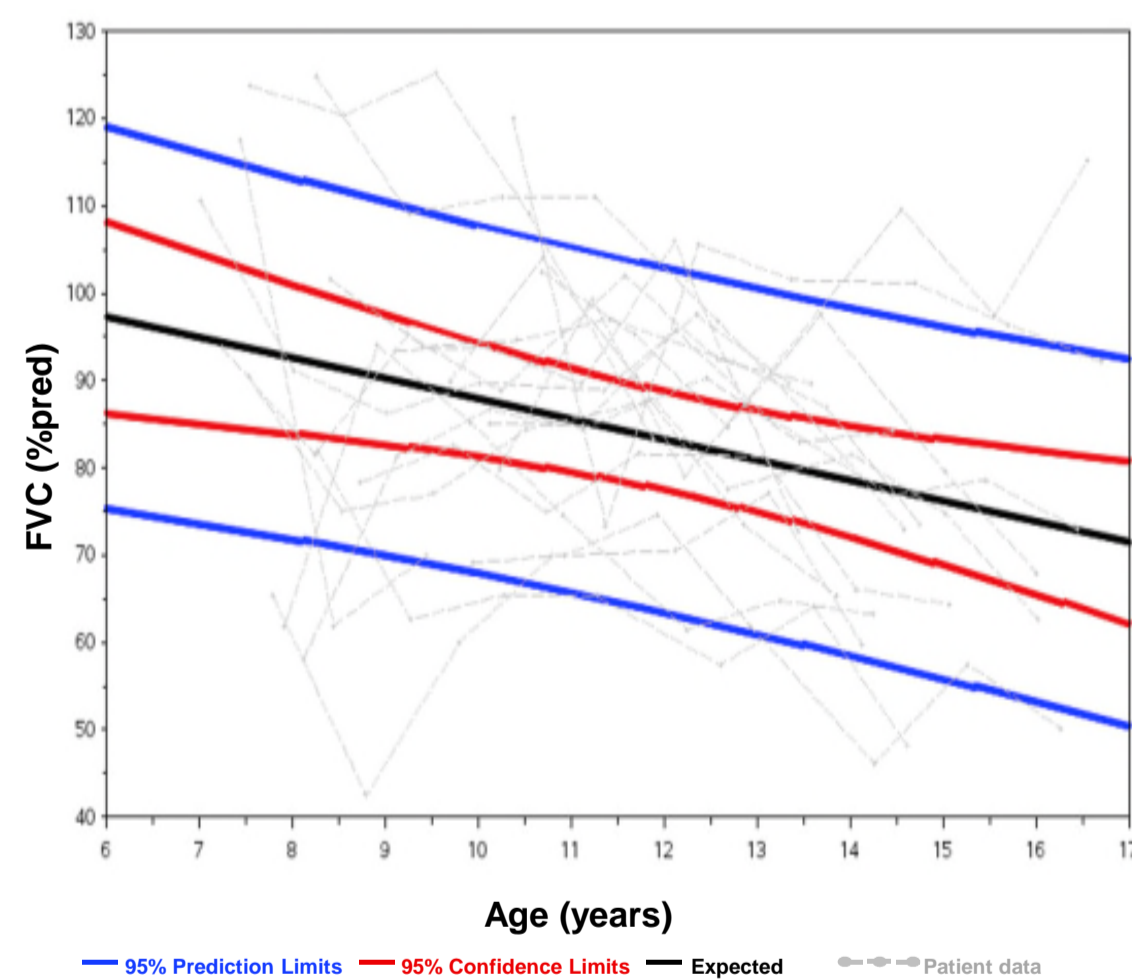
### Impact on the epigenetic effects of the lack of dystrophin

- HDAC inhibition<sup>1</sup>:**
- ✓ 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



## STUDY 43: PULMONARY FUNCTION

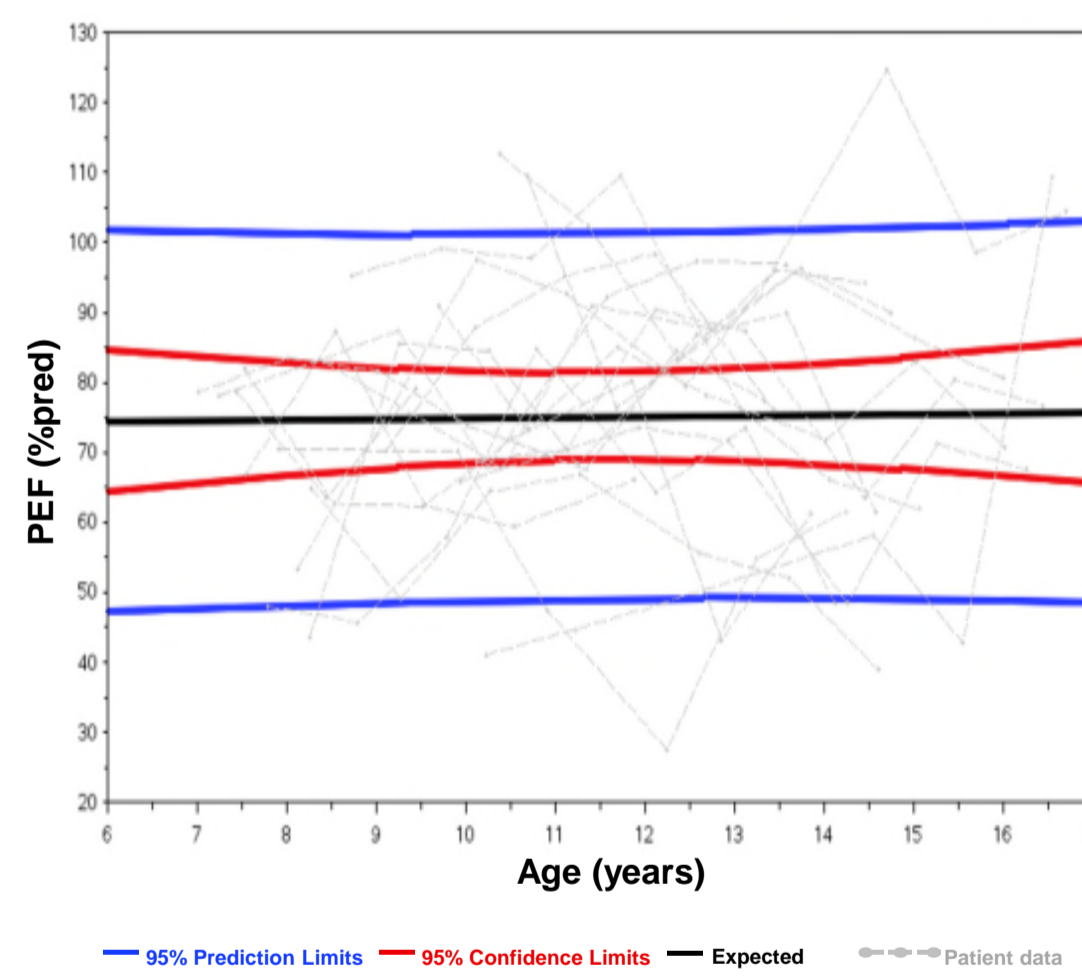
FVC% Predicted: 2.3% yearly decline



A 4 to 6% yearly rate<sup>4, 5, 6</sup> of decline in FVC% Predicted (Forced Vital Capacity) and PEF% Predicted (Peak Expiratory Flow, PEF) 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

PEF% Predicted: no decline



## STUDY 43-51: METHODS

**Study 43 Design** - The study was an open label 2-part, phase 2 clinical trial, which enrolled 20 ambulant DMD boys aged 7 to <11 years. Boys were on a stable dose of corticosteroids for  $\geq 6$  months<sup>2</sup>. The study was extended to allow the continuation of the treatment until 52 month. Participants were transferred to Study 51 and on November 2017, 16 are still on treatment.



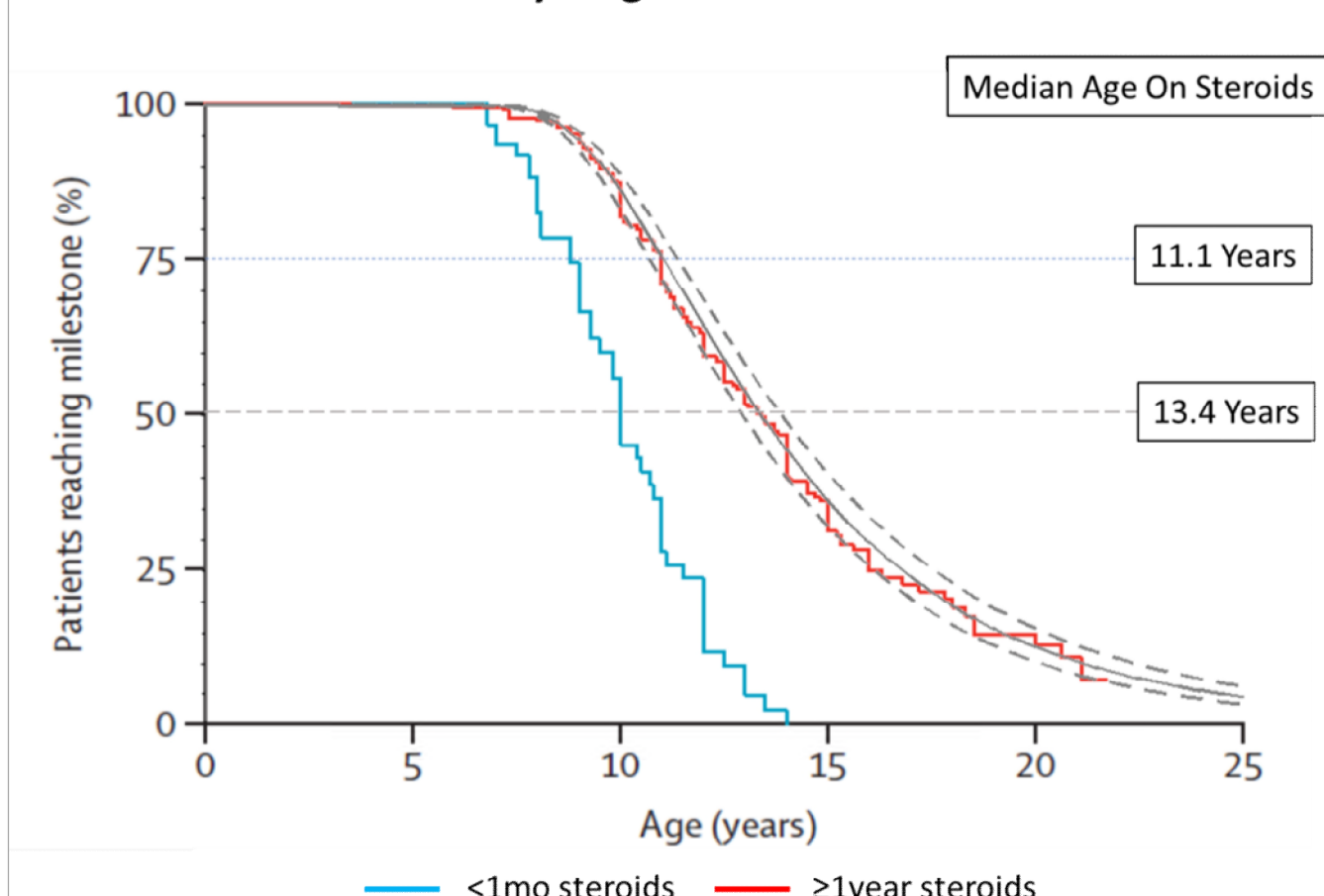
## SAFETY

The most frequent Adverse Events were:

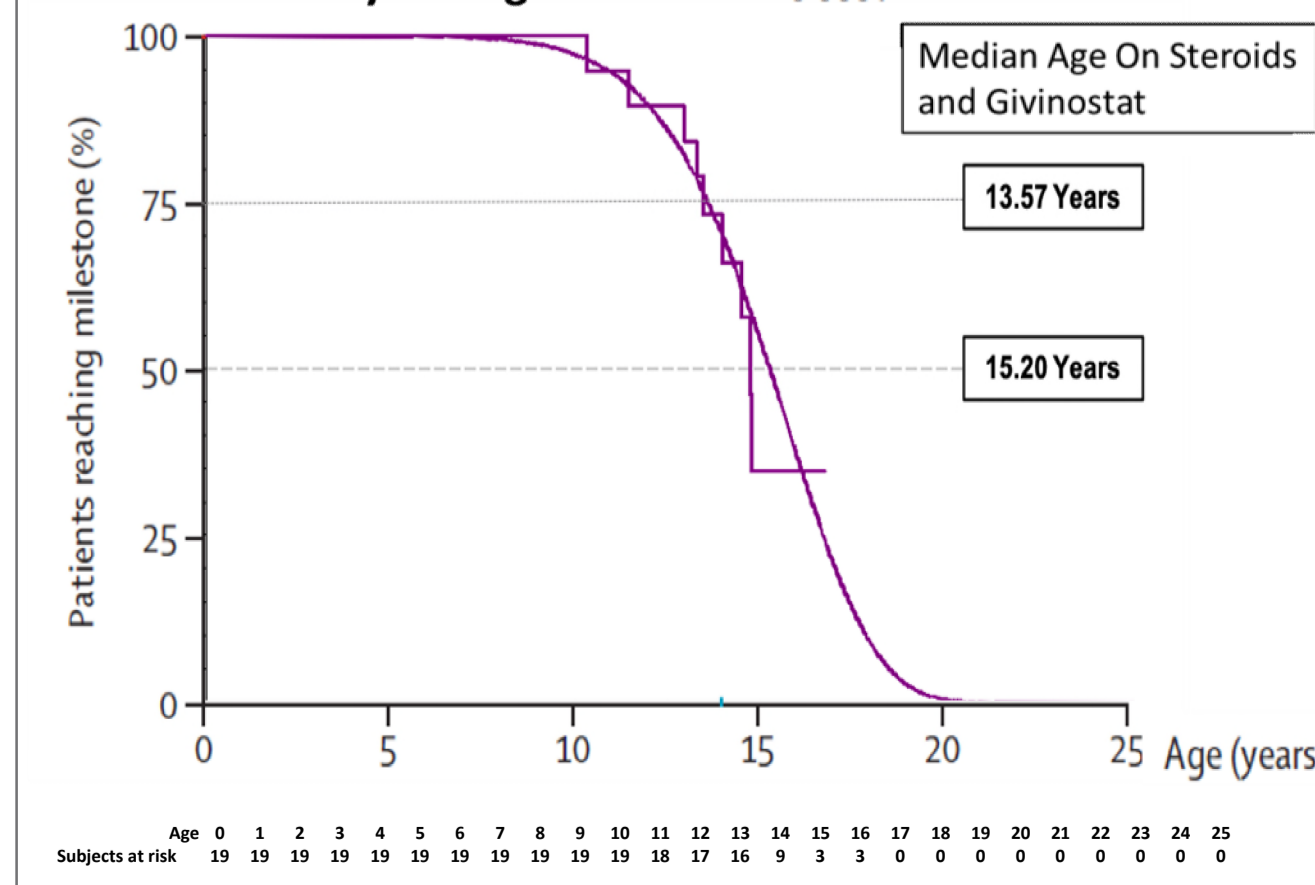
- Platelet count reduction
  - dose-dependent, asymptomatic and fully reversible; may appear within the first weeks of treatment at the non tolerated doses
- Nausea, vomiting, abdominal pain and diarrhea: generally mild to moderate and transient
- Transient and reversible increase of Triglyceride level in some subjects

## STUDY 43-51 (5.4 years of treatment): DISEASE MILESTONE

### CINRG Study<sup>1</sup>: Age at Loss of Ambulation



### Study 43: Age at Loss of Ambulation



Contrasted with the natural history published results (CINRG study<sup>3</sup>) study 43-51 results suggest that the addition of Givinostat to steroid treatment delays disease progression

## CONCLUSION

- Compared to the published natural history data, Givinostat administration appears to be associated with a slowdown of the disease progression
- Givinostat was tolerated at the doses used
- The ongoing Epidys Phase 3 is supported by the preliminary results of the ongoing long safety study

## REFERENCES

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- 2 Bettica et al. Histological effects of givinostat in boys with Duchenne muscular dystrophy. Neuromuscul Disord. 2016;26:643-649.
- 3 McDonald et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. 2018;391(10119):451-461
- 4 Mayer et al. Characterization of pulmonary function in Duchenne Muscular Dystrophy. Paediatr Pulmonol 2015
- 5 Henricson, E. et al. The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. Muscle & nerve 2013; 8 (1), 55-67.
- 6 Kinane et al. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplisen-Treated Patients to Natural History. J Neuromuscul Dis 2018, 5 (1), 47-58.