Development of the histone deacetylases inhibitor Givinostat in Duchenne Muscular Dystrophy

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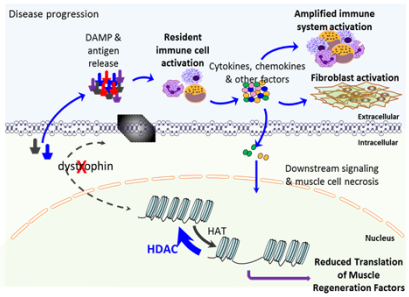
Givinostat Mechanism of Action in Duchenne

Downstream effects of the lack of dystrophin

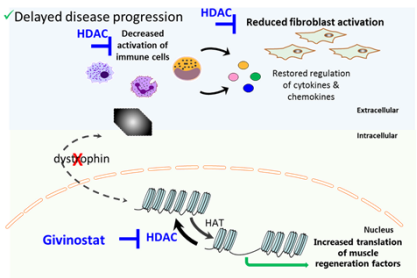
Mechanical effects :
- Increased muscle damage
- Muscle cell membrane instability
- Muscle cell necrosis

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



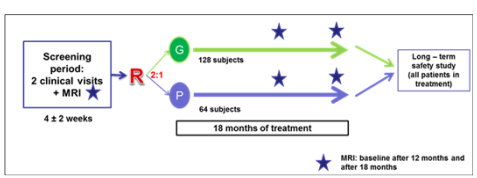
Impact on the epigenetic effects of the lack of dystrophin

HDAC inhibition:
- ✓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



Phase 3 trial: EPIDYS STUDY

Phase 3, multicentre, double blind, placebo controlled (2:1) study in 192 patients to demonstrate that Givinostat oral suspension preserves muscle mass and slows down disease progression. The study design is summarized in figure below. The study is ongoing in USA, Canada and European countries.

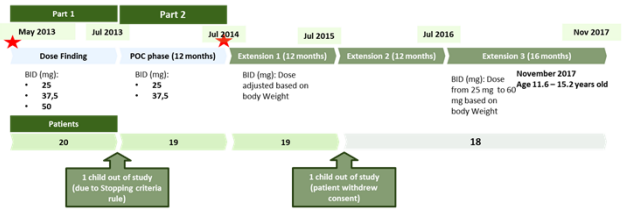


What does participant entail?:
- must be ambulant DMD boys from 6 years of age, on stable corticosteroid for at least 6 months prior to start the treatment and able to perform the 4 stairs climb in no more than 8 seconds and time to stand up in no more than 10 seconds,
- sign Informed Consent

- attend the clinical visits, in total of 15 visits (every 3 months):
  - Blood draw more frequently during the first 3 months: weekly during the first month, every 2 weeks on second month and every 3 months from the third month (in some visits a nurse will perform the blood draw at participant's home)
- muscle tests every 3 months; pulmonary function test baseline, at 12 and 18 months
- thigh muscle MRI: baseline, at 12 and 18 months
- take Givinostat/Placebo Oral suspension twice daily in fed state

STUDY 43: METHODS

Study 43 Design - The study was an open label 2-part, phase 2 clinical trial, which enrolled 20 DMD boys aged 7 to <11 years. Boys were on a stable dose of corticosteroids for ≥ 6 months. The study was extended to allow the continuation of the treatment until 52 month. At baseline and after 12 months of treatment a muscular biopsy was done



Disease Milestones - as of November 2017, 18 boys had been treated with givinostat for 4.4 years allowing an assessment of givinostat effects on disease milestones and on pulmonary function as well as of safety and tolerability

STUDY 43: Primary Endpoint - HISTOLOGY RESULTS

Histology – The amount of muscle (MFAF) and the Cross Sectional Area (CSA) of the muscle fibers were significantly increased after 12 months of treatment, while the amount of fibrotic tissue (Total Fibrosis), Necrosis and Fatty Replacement significantly decreased[2]. Relative changes from baseline in histological parameters are reported in Figure 1.

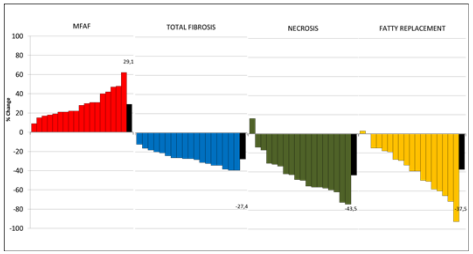
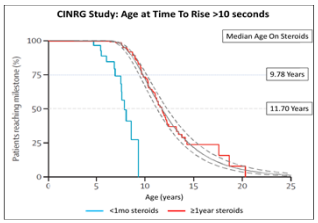
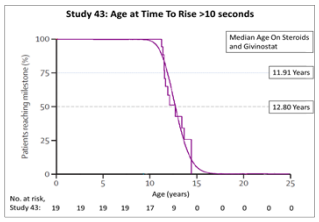


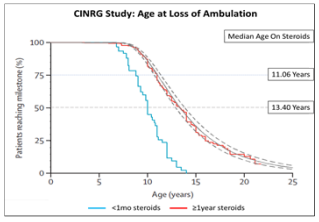
Figure 1 - *Relative change of MFAF, Total Fibrosis, Necrosis and Fatty replacement between end of study and baseline muscle biopsy in all 18 evaluable boys (each colored column represents one boy) and their mean (black column)*

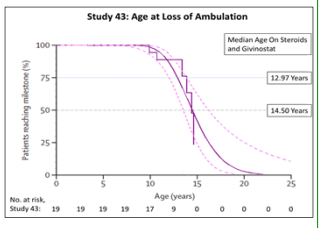
STUDY 43: DISEASE MILESTONES





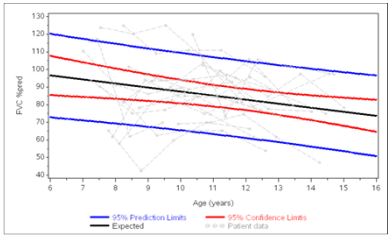
Contrasted with the natural history published results (CINRG study[3]) study 43 results suggest that the addition of Givinostat to steroid treatment delays disease progression



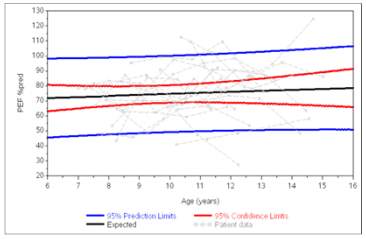


STUDY 43: PULMONARY FUNCTION

FVC% Predicted: 2.3% yearly decline



PEF% Predicted: no decline



- A 4 to 6% yearly rate[4,5,6] 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)

STUDY 43 CONCLUSION

- 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 tolerated 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

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