**Effect of Givinostat, an HDAC inhibitor, on disease milestones in Duchenne Muscular Dystrophy boys**

**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 happens at study visits?**

- **A total of 15 visits (every 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, 45C, QMTR)

**Conclusions**

- 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 extended to allow the continuation of the treatment until 52 month.

**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**
  - **DAMP & integrin release**
  - **Increased muscle regeneration factors**
  - **Fibroblast activation**

**STUDY 43: PULMONARY FUNCTION**

- **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 still on treatment.

**Study 43 Design (Dose Finding)**

- May – July 2013
- Study 51

**Study 43 Design (Givinostat Expansion)**

- July 2014 – Extension
- Nov 2017
- Study 51

**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

**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**