Givinostat in DMD

PPMD Annual Meeting, June 29th 2018
Dr. Paolo Bettica, VP R&D
• 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
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

**Disease progression:**
- DAMP & antigen release
- Resident immune cell activation
- Cytokines, chemokines & other factors
- Fibroblast activation
- Extracellular
- Intracellular
- Reduced Translation of Muscle Regeneration Factors
- Amplified immune system activation
- Downstream signaling & muscle cell necrosis
Givinostat Mechanism of Action in DMD Patients

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

Impact on the epigenetic effects of the lack of dystrophin
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
• Role of Givinostat (ITF2357) in Duchenne Muscular Dystrophy
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• Phase 3 study
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
Givinostat histological results on Muscle Fibres Area Fraction (MFAF), fibrosis, necrosis and fatty replacement are consistent across all children.

*All changes are highly significant (p<0.0005 to <0.0001)
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)

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Month 12</th>
<th>Month 24</th>
<th>Month 36</th>
<th>Month 48</th>
<th>Month 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
<td>Mean (range)</td>
</tr>
<tr>
<td></td>
<td>8.6 (7-10.7)</td>
<td>9.9 (8.2-11.9)</td>
<td>10.9 (9.2-12.9)</td>
<td>12 (10.2-13.9)</td>
<td>13 (11.2-14.9)</td>
<td>13.3 (11.6-15.2)</td>
</tr>
<tr>
<td>N</td>
<td>19</td>
<td>19</td>
<td>19</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
</tbody>
</table>
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, Aaral Cnaan, Heather Gourdish-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)

\(\text{FVC} \%\) Predicted: 2.3% yearly decline

\(\text{PEF} \%\) Predicted: No decline

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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:

<table>
<thead>
<tr>
<th></th>
<th>All AEs N (%)</th>
<th>Drug Related N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
<td>15 (75)</td>
<td>15 (75)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>14 (70)</td>
<td>14 (70)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>11 (55)</td>
<td>9 (45)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>7 (35)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (40)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td>4 (20)</td>
<td>4 (20)</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Stage / Study</th>
<th>Result</th>
</tr>
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<tbody>
<tr>
<td>Histological Effects</td>
<td>✓</td>
</tr>
<tr>
<td>Macroscopic level: MRI data</td>
<td>✓</td>
</tr>
<tr>
<td>Efficacy on function</td>
<td></td>
</tr>
<tr>
<td>Effect on Ambulation</td>
<td>✓</td>
</tr>
<tr>
<td>Respiratory and Upper Limb function data</td>
<td>✓</td>
</tr>
</tbody>
</table>
AGENDA

• Role of Givinostat (ITF2357) in Duchenne Muscular Dystrophy
• Brief review of Givinostat Clinical Data - Phase 2 study
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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

Screening period: 2 clinical visits + MRI 4 ± 2 weeks

G 128 subjects

R 2:1

P 64 subjects

Long – term safety study (all patients in treatment)

MRI: baseline after 12 months and after 18 months
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**: baseline, at 12 and 18 months
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

• 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
Enrollment ongoing: 54 patients randomized
 Patients and Families
 Clinical Sites
 Patients’ associations

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