A Phase 3 Study of Lomitapide, a Microsomal Triglyceride Transfer Protein (MTP) Inhibitor, in Patients with Homozygous Familial Hypercholesterolemia

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The Phase 3 Study Investigators

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12 - H du T Theron - Netcare Private Hospital, Bloemfontein, South Africa
13 - AME du Plessis - Clinical Research Unit, Pretoria, South Africa
22 - D Gaudet - University of Montreal, Chicoutimi, Canada
23 - RA Hegele - Robarts Research Institute, London, Canada
31 - M Averna - Università di Palermo, Italy
32 - A Bondioli - Ospedale Niguarda, Milano, Italy
33 - R Fellin, G Vigna - Università di Ferrara, Italy
35 - C Stefanutti - Università La Sapienza, Roma, Italy

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Homozygous Familial Hypercholesterolemia

12 Y.O. female
HoFH is refractory to currently available lipid lowering drugs
MTP-inhibition reduces apoB-containing lipoprotein production
Pharmacologic MTP inhibition reduces LDL-C levels in HoFH

HoFH Phase 3 Study
Objectives

• To evaluate the efficacy and long term safety of lomitapide in subjects with HoFH on current lipid-lowering therapy

• To generate an adequate database to support regulatory approval and registration for the indication of HoFH
HoFH Phase 3 Study
Main inclusion criteria

• Both genders
• 18 years or older
• Diagnosis of HoFH
  o Clinical criteria
  o Fibroblasts activity
  o Mutations in genes affecting LDL receptor functionality
• Stable concomitant lipid lowering therapies
• Open label, ascending dose of lomitapide
• Low fat diet (<20% fat)
• Careful LFT monitoring
• Liver fat evaluation by MRI + spectroscopy
HoFH Phase 3 Study
Subject Disposition

32 screened

31 entered Run-in

29 entered Efficacy Phase

23 completed Efficacy Phase (Week 26)

23 Completed Safety Phase (Week 78)

6 Discontinuations:
- Adverse Event (n=4)
- Withdrew consent (n=1)
- Noncompliance (n=1)
### HoFH Phase 3 Study

**Subjects Characteristics**

<table>
<thead>
<tr>
<th>Subjects characteristics at baseline (n=29)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean±SD (range)</td>
<td>31 ± 11 (18-55)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>16 (55.2%)</td>
</tr>
<tr>
<td>Caucasians, n (%)</td>
<td>25 (86.2%)</td>
</tr>
<tr>
<td>Genetic diagnosis, n (%)</td>
<td>29 (100%)</td>
</tr>
<tr>
<td>CVD, n (%)</td>
<td>27 (93%)</td>
</tr>
<tr>
<td>Statin therapy, n (%)</td>
<td>26 (90%)</td>
</tr>
<tr>
<td>Other lipid lowering drugs, n(%)</td>
<td>23 (79%)</td>
</tr>
<tr>
<td>Apheresis, n (%)</td>
<td>18 (62%)</td>
</tr>
</tbody>
</table>
# HoFH Phase 3 Study

## Subjects characteristics

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>6 (20.7%)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>1 (3.4%)</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>25.8 ± 5.4</td>
</tr>
<tr>
<td>BP sys, mmHg</td>
<td>118 ± 14</td>
</tr>
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<td>BP dia, mmHg</td>
<td>63 ± 9</td>
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<td>LDL-C, mg/dl</td>
<td>336 ± 114</td>
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Efficacy
Pharmacologic MTP inhibition reduces LDL-C levels in HoFH

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 26</th>
<th>% Change (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>430 ± 135</td>
<td>236 ± 112</td>
<td>-46 (-56, -35)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C</td>
<td>336 ± 114</td>
<td>168 ± 96</td>
<td>-50 (-62, -39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>nonHDL-C</td>
<td>386 ± 132</td>
<td>196 ± 107</td>
<td>-50 (-61, -39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TG</td>
<td>92 (32-253)</td>
<td>43 (10-149)</td>
<td>-45 (-61, -29)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>apoB</td>
<td>259 ± 80</td>
<td>133 ± 71</td>
<td>-49 (-60, -38)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Pharmacologic MTP inhibition reduces LDL-C levels in HoFH
Pharmacologic MTP inhibition reduces LDL-C levels in HoFH

- At week 26:
  - 8 patients < 100 mg/dl
  - 1 patient < 70 mg/dl
- At any time during the study:
  - 16 patients < 100 mg/dl
  - 9 patients < 70 mg/dl

- At week 26, 13 subjects were receiving apheresis. During the safety phase:
  - 7 patients: unchanged apheresis treatment
  - 3 patients: reduced frequency
  - 3 patients: stopped apheresis permanently
Pharmacologic MTP inhibition reduces LDL-C levels in HoFH

Data are mean, 95%CI (n=23)
Pharmacologic MTP inhibition does not permanently affect HDL-C levels in HoFH.

![Graph showing HDL-C levels over study weeks with Efficacy Phase (44±11 mg/dL) and Safety Phase (43±12 mg/dL).]
Safety Analysis
### HoFH Phase 3 Study
Treatment Emergent Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event Category</th>
<th>n of subjects (%) weeks 0-26</th>
<th>n of subjects (%) weeks 26-78</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=29</td>
<td>N=23</td>
</tr>
<tr>
<td>Any adverse event</td>
<td>27 (93.1)</td>
<td>21 (91.3)</td>
</tr>
<tr>
<td>GI Disorders</td>
<td>27 (93.1)</td>
<td>17 (73.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (79)</td>
<td>8 (35)</td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (62)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Lab abnormalities</td>
<td>15 (51.7)</td>
<td>10 (43.5)</td>
</tr>
<tr>
<td>ALT elevation &gt;5 x ULN</td>
<td>4 (13.8)</td>
<td>2 (9.0)</td>
</tr>
</tbody>
</table>
HoFH Phase 3 Study
Transaminases levels

Data are mean, 95%CI (n=23)
HoFH Phase 3 Study
Hepatic Fat Content

N=20
Data are mean, 95%CI
HoFH Phase 3 Study
Conclusions

- Treatment with the MTP inhibitor lomitapide is very effective in lowering LDL-C in HoFH in concomitant therapy
- Lomitapide is generally well tolerated in HoFH in the presence of low fat diet and dose escalation scheme
- Lomitapide is associated with a minimal to moderate hepatic fat accumulation at week 26 that stabilized by the end of the 78 week treatment period
Acknowledgments

Sites

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