MTP inhibition for hoFH and chylomicronemia?

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Agenda

• Characteristics and treatment of HoFH
• Clinical study of MTP inhibitor in HoFH
• MTP inhibitor for chylomicronemia
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  • Clinical study of MTP inhibitor in HoFH
  • MTP inhibitor for chylomicronemia
HoFH Overview

• HoFH is a serious genetic disease characterized by significantly elevated LDL-C levels, xanthomas and premature atherosclerosis.

• There are well established clinical characteristics of HoFH; however, the clinical presentation of the disease may vary.

• HoFH is underdiagnosed and undertreated.
Prevalence of HoFH

- Prevalence of HoFH was historically reported as 1 in 1,000,000.

- Recent data estimate the prevalence of FH (HeFH) of 1 in 200 in the Dutch population, which would give a calculated prevalence of HoFH of ~ 6 in 1,000,000.

- The prevalence of HoFH in a given region may be highly dependent on its demographics as founder effects make the prevalence of HoFH more common in certain populations who are descended from relatively small founding populations.
  - 1/270,000 in the French-Canadian population,
  - 1/640,000 in the Dutch population,
  - 1/100,000 in the Lebanese population,
  - 1/30,000 in a South African Afrikaners population
Known Molecular causes of HoFH

Where a mutation can be found:
~95% are due to mutations in \textit{LDLR} gene
~5\% due to other mutations in \textit{APOB}, \textit{PCSK9} and \textit{LDLRAP1 (ARH)} genes

- **LDLR** (chr 19p13)
  Primary familial hypercholesterolemia
  OMIM: 143890

- **APOB** (chr 2p24)
  Familial defective Apo B
  OMIM: 144010

- **PCSK9** (chr 1p32)
  Proprotein convertase subtilisin/kexin type 9
  OMIM: 603776

- **LDLRAP1 (ARH)** (chr 1p36)
  Autosomal recessive hypercholesterolemia
  OMIM: 603813
A number of combinations of genetic mutations can result in the clinical phenotype of HoFH:

- **True (simple) homozygotes**: 2 identical mutations on both copies of LDLR gene
- **Compound heterozygotes**: 2 different mutations on both copies of the LDLR gene
- **Double heterozygotes**: 2 different mutations on two different genes (e.g. LDLR, APO B)
- **Autosomal recessive hypercholesterolemia (ARH)**: 2 mutations in the autosomal recessive LDLRAP1 gene

The effect of different mutations on LDL-C metabolism is variable:

- Some mutations lead to a total lack of LDLR activity (<2% activity, receptor-negative patients)
- Others mutations severely reduce the activity of LDLRs (<30% activity, receptor-defective patients)
Figure 4  Phenotypic variability in homozygous familial hypercholesterolaemia. For full explanation and relevant literature refer to Supplementary material online. LDL, low-density lipoprotein; APOB, apolipoprotein B; PCSK9, pro-protein convertase subtilisin/kexin type 9; LDLRAP1, LDL receptor adaptor protein 1 (i.e. ARH, autosomal recessive hypercholesterolaemia).
Mechanisms of conventionally used lipid lowering drugs

HoFH patients have absent or reduced LDL-R activity

apo B-100

MTP

Nascent VLDL

LDLR

Statin
Ezetimibe
Resin
PCSK9 inhibitor

VLDL

LDL
Cumulative cholesterol years and development of severe atherosclerosis

- **Homozygous FH**
  - Start high dose statin after 12.5 years
  - Threshold for CHD after 35 years

- **Heterozygous FH**
  - Start low dose statin
  - Start high dose statin after 48 years
  - Threshold for CHD after 53 years

- **Without FH**
  - Start low dose statin
  - Threshold for CHD after 55 years

**Adapted from Steve Humphries 2013**

- Female sex
- Smoking
- Hypertension
- Diabetes
- ↑Triglycerides
- ↓HDL-C
- ↑Lipoprotein(a)
Statins have limited effectiveness in HoFH

- Statins have been the mainstay of therapy in HoFH even when the LDL-R is absent\(^1\)
  - Reductions in all-cause mortality are evident\(^2\)
  - Only modest reductions in LDL-C (10–25%) are observed
  - Addition of ezetimibe can improve the effectiveness of statins\(^3\)

Treatment of HoFH

- High dose statins, ezetimibe, and probucol
- LDL apheresis
Fluctuation of LDL-C Levels Following a Single Apheresis Procedure
Aortography of HoFH (female)

Age, years | 5 | 15 | 24

2 y.o. Angina pectoris
5 y.o. Receives plasma exchange
10 y.o. weekly lipoprotein apheresis;
CABG operation performed at ages 10 and 15 years
Aortography of Patient HoFH (Female)

| Age, years | 5 | 11 |
Aortography of HoFH (Male)

<table>
<thead>
<tr>
<th>Age, years</th>
<th>5</th>
<th>10</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV-Ao PD, mmHg</td>
<td>0</td>
<td>70</td>
<td>50</td>
</tr>
</tbody>
</table>

The patient had simple plasma exchange from the age of 5 to 10. Lipoprotein apheresis was performed from the age of 10.

PD, pressure difference; AVR, aortic valve replacement
Although weekly lipoprotein apheresis was applied, aortic stenosis developed and AVR surgery was performed at age 32 years.

<table>
<thead>
<tr>
<th>Age, years</th>
<th>9</th>
<th>19</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV-Ao PD, mmHg</td>
<td>12</td>
<td>96</td>
<td>170</td>
</tr>
</tbody>
</table>
Summary 1

- HoFH patients have mutation in the molecules in LDL receptor pathway.
- LDL-C levels in HoFH patients cannot be controlled well by the drugs that act via LDL receptor.
- Lipoprotein apheresis treatment is not enough to prevent development of atherosclerosis in HoFH.
Agenda

• Characteristics and treatment of HoFH
• Clinical study of MTP inhibitor in HoFH
• MTP inhibitor for chylomicronemia
Microsomal Triglyceride Transfer Protein (MTP)

- **MTP** is an intracellular lipid-transfer protein found in the lumen of the endoplasmic reticulum (ER) responsible for binding and shuttling lipid molecules between membranes.
- **MTP** is necessary for the proper assembly and secretion of apo B-containing lipoproteins in the liver and intestines.
Mechanism of Action of MTP Inhibitors

- Lomitapide binds and inhibits MTP, thereby preventing the assembly of apo B-containing lipoproteins in hepatocytes and enterocytes.
- This inhibits the synthesis of VLDL and chylomicrons.
- Inhibition of VLDL results in reduced LDL-C in the plasma.

Hypothesized Clinical Effects of MTP Inhibition

Based on the physiological role of MTP, inhibition of MTP could be anticipated to have the following outcomes:

• **Efficacy**
  – Potential to produce a significant reduction in VLDL synthesis and, subsequently, LDL levels.
  – Potential to produce a significant reduction in chylomicrons and, subsequently, chylomicron remnant levels, which may indirectly lower LDL-C.
  – Potential to produce a significant reduction in apo B levels.
Hypothesized Clinical Effects of MTP Inhibition

• **Safety and Tolerability**
  – Potential to produce GI side effects.
  – Potential for increased hepatic fat (triglycerides).
  – Potential to reduce absorption of fat-soluble vitamins (e.g., vitamin E) and essential fatty acids (e.g., omega 3 fatty acids).
Efficacy and safety of lomitapide were evaluated in a Phase 3 clinical study:

- 78-week, single-arm, open-label study involving 29 adults with HoFH.
- Primary endpoint: Percent change in LDL-C from baseline to Week 26.
- Efficacy was assessed in the intent-to-treat (ITT) population utilizing a last observation carried forward (LOCF) analysis.
- Age range of patients included in the study was between 18 and 55 years.

Phase 3 study design

- 6-week run-in phase to stabilize diet and background lipid-lowering therapy.
- Dose escalated from 5 mg to maximum tolerated dose (MTD) during efficacy phase (26 weeks).
- Safety phase: weeks 26–78, to evaluate longer-term safety at MTD.
- Low-fat diet (<20% energy as fat) throughout study; concomitant therapy fixed through week 26, with ability to change background therapy weeks 26–78.

Phase 3 Study – Entry Criteria

Patients must have been diagnosed as having functional HoFH defined by at least one of the following criteria:

- Untreated TC > 500 mg/dL (>12.9 mmol/L) and TG < 300 mg/dL (<7.8 mmol/L) and both parents have documented TC > 250 mg/dL (>6.5 mmol/L)

- Documented functional mutation(s) in both LDL receptor alleles or alleles of other genes known to affect LDL receptor functionality

- Skin fibroblast LDL receptor activity < 20% normal

Phase 3 – Patient Disposition

32 Patients Screened

31 Entered Run-in

29 Entered Efficacy Phase

23 Completed Efficacy phase (Week 26)

23 Completed Safety Phase (Week 78)

6 Discontinuations
- Adverse events (n=5)
- Noncompliance with protocol (n=1)

# Phase 3 Study – Patient Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Min, Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (years)</td>
<td>30.7 ± 10.56</td>
<td>18.0, 55.0</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>16/13</td>
<td></td>
</tr>
<tr>
<td>Race (Caucasian/Asian/Black/Other)</td>
<td>25/2/1/1</td>
<td></td>
</tr>
<tr>
<td>Mean (SD) BMI (kg/m²)</td>
<td>25.8 ± 5.4</td>
<td>19.3, 41.3</td>
</tr>
<tr>
<td>Mean (SD) baseline LDL-C (mg/dL and mmol/L)</td>
<td>336 ± 113.7 8.7 (3.0)</td>
<td>152, 564</td>
</tr>
<tr>
<td>Receiving apheresis, n (%)</td>
<td>18 (62%)</td>
<td></td>
</tr>
<tr>
<td>Receiving lipid lowering drugs (LLDs), n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>27 (93%)</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe (all in combination with statins)</td>
<td>22 (76%)</td>
<td></td>
</tr>
</tbody>
</table>

Phase 3 Study Results – Change in LDL-C Through Week 78

(Completer Population, N=23)

Mean % Change from Baseline (95%CI)

Efficacy Phase | Safety Phase

Study Week

Mean Dose (LOCF) (mg): 45

Phase 3 Study Results – Secondary Endpoints

Percent Changes from Baseline in Lipids and Lipoproteins at week 26 (N=29)

<table>
<thead>
<tr>
<th></th>
<th>Total Cholesterol (TC)*</th>
<th>Apo B*</th>
<th>Non-HDL-C*</th>
<th>VLDL-C*</th>
<th>Triglycerides (TG)*</th>
<th>HDL-C*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent Change</td>
<td>-36%</td>
<td>-39%</td>
<td>-40%</td>
<td>-29%</td>
<td>-45%</td>
<td>-7%</td>
</tr>
</tbody>
</table>

Mean (SD)

<table>
<thead>
<tr>
<th></th>
<th>mg/dL</th>
<th>mmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>258 (118)</td>
<td>6.7 (3.1)</td>
</tr>
<tr>
<td>Apo B</td>
<td>148 (74)</td>
<td>3.8 (1.9)</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>217 (113)</td>
<td>5.6 (2.9)</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>13 (9)</td>
<td>0.3 (0.2)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>57</td>
<td>0.6</td>
</tr>
<tr>
<td>HDL-C</td>
<td>41 (13)</td>
<td>1.1 (0.3)</td>
</tr>
</tbody>
</table>

*p value on the mean percent change from baseline based on paired t-test
*Median values are presented for TG; p-value is based on the mean percent change.

LDL-C Treatment Goal Attainment in Phase 3

<table>
<thead>
<tr>
<th>Time Point</th>
<th>LDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;100 mg/dL (&lt;2.59 mmol/L)</td>
</tr>
<tr>
<td>Baseline (N=29)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>At one or more time point on treatment with lomitapide (N=29)</td>
<td>16 (55%)</td>
</tr>
</tbody>
</table>

**Recognized Global LDL-C Treatment Goals**

- <100 mg/dL (<2.59 mmol/L) for patients at high-risk of CHD\(^1\text{-}^3\)
- <70 mg/dL (<1.81 mmol/L) for patients with known CHD\(^2,^3\)

*If the target goal cannot be achieved in a given patient, aim for at least a ≥50% reduction\(^1\text{-}^4\)*

Summary of Alterations in Apheresis Treatment During the Phase 3 Safety Phase

- 13 (57%) patients were receiving apheresis at the start of the safety phase.
- 6 patients had changes to their apheresis regimen.

<table>
<thead>
<tr>
<th>Patients Reducing Frequency of Apheresis Treatments</th>
<th>Patients Stopping Apheresis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety phase (Week 26-78)</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

## Phase 3 – Adverse Events in >10% of Patients

(Safety Population, N=29)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23 (79)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (65)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11 (38)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10 (34)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Constipation</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Flatulence</td>
<td>6 (21)</td>
</tr>
<tr>
<td>Gastroesophageal reflux disease</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Defecation urgency</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Rectal tenesmus</td>
<td>3 (10)</td>
</tr>
</tbody>
</table>

Phase 3 – Gastrointestinal Adverse Events

(Safety Population, N=29)

Phase 3 – Aminotransferase and Bilirubin Levels
(Safety Population, N=29)

ULN for ALT: females is 33 and males is 40 U/L.
ULN for AST: females is 36 and males is 43 U/L.
ULN for bilirubin (all patients) is 1.1 mg/dL (18.81 µmol/l).

Peak Aminotransferase Levels in Phase 3

(Safety Population, N=29)

<table>
<thead>
<tr>
<th>ALT and/or AST Levels†</th>
<th>Over Entire Study N=29</th>
<th>Efficacy Phase 0-26 Weeks N=29</th>
<th>Safety Phase 26-78 Weeks N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2x ULN</td>
<td>15 (52%)</td>
<td>17 (59%)</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>&gt;2x ULN - ≤3x ULN</td>
<td>4 (14%)</td>
<td>4 (14%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>&gt;3x ULN - &lt;5x ULN</td>
<td>6 (21%)</td>
<td>4 (14%)</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>≥5x ULN - &lt;10x ULN</td>
<td>3 (10%)</td>
<td>3 (10%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>≥10x ULN</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

† ULN for ALT: 33 U/L (females); 40 U/L (males); ULN for AST: 36 U/L (females); 43 U/L (males).

- 6/29 patients did not experience any ALT or AST elevations during the study.
- 3 of the 6 patients were on study for the full 78 weeks.

Phase 3 – Hepatic Fat Content as Measured by MRS

(Safety Population, N=29)

<table>
<thead>
<tr>
<th>Week</th>
<th>N</th>
<th>Mean (%)</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>22</td>
<td>0.97</td>
<td>0 to 3.8</td>
</tr>
<tr>
<td>26</td>
<td>21</td>
<td>8.32</td>
<td>0.8 to 33.6</td>
</tr>
<tr>
<td>56</td>
<td>20</td>
<td>6.97</td>
<td>0.4 to 37.7</td>
</tr>
<tr>
<td>78</td>
<td>20</td>
<td>7.80</td>
<td>0.6 to 19.0</td>
</tr>
</tbody>
</table>

Summary 2

• 4 of 29 patients experienced transient and reversible ALT elevations ≥5x ULN that were managed by dose reduction or temporary interruption.

• ALT/AST elevations were clinically manageable using the dose reduction/ dose interruption algorithm specified in the study protocol.

• No significant elevations in bilirubin or alkaline phosphatase were observed.

• Hepatic fat increased modestly during the dose escalation phase and then stabilized.

• No subjects discontinued lomitapide treatment based on liver function test elevations or hepatic related adverse events.

Agenda

• Characteristics and treatment of HoFH
• Clinical study of MTP inhibitor in HoFH
• MTP inhibitor for chylomicronemia
Case report

• The patient was hospitalized for pancreatitis at age 15 years.
• Low fat diet, gemfibrozil, ω-3 fatty acids, niacin; no benefit
• Recurrent pancreatitis required 12 hospitalizations for 11 years.
• At age 44 years, she had a near fatal episode of pancreatitis.
• Serum TG levels were usually higher than 2,000.
• She had homozygous for LPL deficiency.

From: **Severe Hypertriglyceridemia With Pancreatitis: Thirteen Years’ Treatment With Lomitapide**


Figure Legend:

Serum Fasting Triglyceride Concentrations at Baseline (B) and During the First Year of Treatment With LomitapideThe dose of lomitapide was adjusted to balance efficacy and tolerability. The patient’s triglyceride level when receiving 12.5 mg/d averaged 2110 mg/dL, when receiving the alternating dose regimen of 12.5 mg/d and 25 mg/d averaged 1416 mg/dL, and when receiving 25 mg/d averaged 371 mg/dL. Discontinued indicates temporary cessation of lomitapide. (To convert triglycerides to millimoles per liter, multiply by 0.0113.)
Serum Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) at Baseline and During 13 Years’ Treatment With Lomitapide

The upper limits of normal were 40 U/L for ALT (A) and 35 U/L for AST (B). Findings of the liver biopsy described in more detail in the subsection titled “Hepatic Toxicity of Lomitapide.” B indicates baseline. (To convert ALT and AST to microkatal/s per liter, multiply by 0.0167.)
• One case of chylomicronemia with LPL deficiency was reported.
• She had severe pancreatitis for many years.
• Serum TG level and pancreatitis were controlled by administration of lomitapide.
• After administration of lomitapide for 13 years, hepatic toxicity was observed.