The Role of Microsomal Triglyceride Transfer Protein Inhibition in the Management of HoFH

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Disclosures

- Consultant/speaker: Aegerion, Genzyme, Merck, Liposcience, AstraZeneca
Objectives

- To understand the role of microsomal triglyceride transfer protein (MTP) in the production of apoB-containing lipoproteins, including VLDL, IDL, LDL, and chylomicrons

- To discuss the role of MTP deficiency in the etiology, symptoms, and findings in abetalipoproteinemia

- To examine the role of MTP inhibition to reduce the production of apoB-containing lipoproteins in the management of homozygous familial hypercholesterolemia

- To review the safety and efficacy of lomitapide, the first MTP inhibitor approved for treatment of HoFH
HoFH Case Study
Case Study: BA

- Currently 50 yo WM
- First seen in his 30’s by lipidologist
- Strong family history of hyperlipidemia, premature CAD
- History of TC 600+ mg/dl, LDL-C >450+ mg/dl
- Frustrated by minimal response to available therapies, discontinued all meds until...
- CABG x 3 at age 39
Case Study: BA

- **2005**: on rosuvastatin 40 mg, ezetimibe 10 mg
  - TC 257, HDL-C 49, LDL-C 184, TG 120
  - Declined LDL apheresis
- **2008**: rosuvastatin 40, EZE 10, colesevelam 3.75 g, niacin ER 1 g
  - TC 231, HDL-C 50, LDL-C 163, TG 91
  - Recurrent angina, NSTEMI, lesion distal to graft not approachable by PCI, recommended optimal medical therapy
Case Study: BA

- April, 2008: on rosuvastatin 40 mg, EZE 10 mg, colesevelam 3.75 g
  - Developed intolerable flushing on niacin ER
  - TC 255, HDL-C 44, LDL-C 185, TG 129
  - Declined LDL apheresis

- July, 2008: rosuvastatin 40 mg, EZE 10 mg, colesevelam 3.75 g
  - TC 259, HDL-C 53, LDL-C 187, TG 95
  - Consents to LDL apheresis
Microsomal triglyceride transfer protein (MTP)

- Intracellular lipid transfer protein
- Localized in the endoplasmic reticulum of hepatocytes and enterocytes
- Critical role in early stage of lipoprotein assembly,
  - Transfers TG, CE, and PL onto nascent apoB as it enters the lumen of the ER, shuttling individual lipid molecules between membranes
  - Acts as a chaperone to assist in apoB folding
- Necessary for formation of chylomicrons, VLDL and downstream remnants
- MTP expression can enhance formation of apoB-containing lipoproteins
  - Appears to control number of particles rather than lipid composition of particles

VLDL and Chylomicron Synthesis

Liver Cell

Intestinal Epithelial Cell

Blood Vessel

Microsomal triglyceride transfer protein and apoB regulation

- Secretion of apo B and apo B-containing particles depends on balance between degradation and lipoprotein assembly via MTP
- Apo B gene is constitutively expressed (rate of synthesis remains constant)
- apoB binds with high affinity to MTP
- If nascent apo B molecule does not acquire sufficient lipid it will be rapidly degraded in the ER

'A' FOR ABETALIPOPROTEINEMIA
Microsomal triglyceride transfer protein

- MTP deficiency—abetalipoproteinemia
  - Mutation in MTP gene identified as cause in 1992, 1993
  - Rare autosomal recessive disorder (1:70,000,000—males>females)
  - Undetectable MTP activity in hepatocytes and enterocytes
  - Trace levels of apoB-containing lipoproteins
  - Characterized by fat malabsorption, steatorrhea, hepatic steatosis
    - Also acanthosis, atypical retinitis pigmentosa, and neuromuscular disorders of vitamin malabsorption prior to water-soluble vitamin E supplementation

Science. 1992;258:999-1001
Expert Opin Therap Targets. 2007;11:181-189
Microsomal triglyceride transfer protein inhibition

- Given the central role of MTP in lipoprotein metabolism, assembly and secretion of VLDL and chylomicrons
  - Inhibitors of MTP as lipid-regulating agents

- Lomitapide (BMS-201038/AEGR-733)
  - Synthetic small molecule
  - Benzimidazole-based analogue

Science. 1992;258:999-1001
Expert Opin Therap Targets. 2007;11:181-189
Predicted Effects of MTP Inhibition

Liver Cell

↑TG results in ↑ hepatic fat

Intestinal Epithelial Cell

↑TG contributes to GI tolerability issues

Blood Vessel

Lumen

ER

Cytoplasm

Apo B100 Degraded

MTP

TG

Lower VLDL, LDL, chylomicrons, and chylomicron remnants

Apo B48 Degraded

Lomitapide: POC, Dose-escalation study

Inhibition of Microsomal Triglyceride Transfer Protein in Familial Hypercholesterolemia

Marina Cuchel, M.D., Ph.D., LeAnne T. Bloedon, M.S., R.D., Philippe O. Szapary, M.D., Daniel M. Kolansky, M.D., Megan L. Wolfe, B.S., Antoine Sarkis, M.D., John S. Millar, Ph.D., Katsunori Ikewaki, M.D., Evan S. Siegelman, M.D., Richard E. Gregg, M.D., and Daniel J. Rader, M.D.
Lomitapide: Dose-escalation study in HoFH

- 6 HoFH patients (3 men, 3 women)
- 18-40 years of age
- All lipid therapies suspended at least 4 weeks prior to baseline visit
- Doses: 0.03, 0.1, 0.3, and 1.0 mg/kg per day
- Duration: 4 weeks
- Dietary counseling: 10% of energy from fat (actual 16.7%, range 10-30%)
- Hepatic MRI: baseline, after 4 weeks of therapy, 4 weeks after discontinuation of therapy
Lomitapide: Dose-escalation study in HoFH

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Body-Mass Index*</th>
<th>Cardiovascular Disease†</th>
<th>LDL-Receptor Gene Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>18</td>
<td>56.1</td>
<td>24.3</td>
<td>Absent</td>
<td>delEx3-6/delEx3-6</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>18</td>
<td>59.0</td>
<td>25.3</td>
<td>Absent</td>
<td>1877delA/?</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>35</td>
<td>85.4</td>
<td>27.7</td>
<td>Present</td>
<td>652delG/GT/652delG/GT</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>40</td>
<td>77.3</td>
<td>30.1</td>
<td>Present</td>
<td>Ser156Leu/Ser156Leu</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>22</td>
<td>60.1</td>
<td>18.5</td>
<td>Absent</td>
<td>Cys660Xaa/Cys660Xaa</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>21</td>
<td>64.0</td>
<td>23.2</td>
<td>Absent</td>
<td>Cys660Xaa/Cys660Xaa</td>
</tr>
</tbody>
</table>

* The body-mass index is the weight in kilograms divided by the square of the height in meters.
† Patients 3 and 4 had symptomatic coronary artery disease that was confirmed by coronary angiography. Patients 1, 2, 5, and 6 had no symptoms of cardiovascular disease and were regularly evaluated with the use of noninvasive testing (and, if appropriate, coronary angiography), without evidence of obstructive coronary disease.
Lomitapide: Dose-escalation study in HoFH

Figure 1. Mean Percent Change from Baseline Levels of Total Cholesterol, LDL Cholesterol, and Apolipoprotein B after Receipt of Four Doses of BMS-201038, Each for 4 Weeks.

I bars indicate standard deviations.
Lomitapide: Dose-escalation study in HoFH

- Substantial variability in hepatic fat accumulation
- 2 patients with greatest increase in hepatic fat and ALT: one with severe hypertriglyceridemia, one with significant alcohol intake
Lomitapide: Pivotal Phase 3 trial
Single-arm, open label multicenter Phase 3 Study of lomitapide in HoFH

- Multicenter study of 29 patient with HoFH
  - 11 centers: US, Canada, South Africa, Italy
  - Primary endpoint: % change in LDL-C
  - 32 screened, 31 completed run-in phase, 29 completed efficacy phase (26 weeks), and 23 completed full study (78 weeks)
  - Mean age 30.7 (18-55) yrs
  - 25 Caucasian, 2 Asian, 1 AA, 1 other
  - Men: 16, Women: 13
  - Cardiovascular disease: 27 (21 valvular disease, 21 CAD)

Lancet 2013;381:40-46
Single-arm, open label multicenter Phase 3 Study of lomitapide in HoFH

- All confirmed HoFH by genotype:
  - 28 homozygotes or compound heterozygotes for mutations in LDL-R gene
  - One homozygous for ARH (LDLRAP1) gene mutation

- Mean LDL-C 336, TC 430, apoB 259, HDL-C 44, TG 92

- Statins 93% (27), ezetimibe 76% (22), LDL apheresis 62% (18)

- Median dose of lomitapide 40 mg

- Hepatic MRI at baseline and 6 month intervals (3 patients had contraindications—CT or US if indicated)

Lancet 2013;381:40-46
Single-arm, open label multicenter Phase 3 Study of lomitapide in HoFH

- The 78 week study had three time periods (cont.):

- **Run-in period**: stabilization of concomitant lipid-lowering therapies, including apheresis, daily dietary supplement of vitamin E and essential fatty acids, low-fat diet <20% energy from fat
- **Efficacy phase**: forced dose-titration to 60 mg QD or until maximum tolerated/safe dose. No alterations of other LLT permitted.
- **Safety phase**: Alteration of LLT permitted.

Single-arm, open label multicenter Phase 3 Study of Iomitapide in HoFH

Figure 1: Mean percent changes in LDL cholesterol, total cholesterol, and ApoB levels from baseline to week 26 (end of efficacy phase)
Data available at each time point are expressed as mean (SD).
Single-arm, open label multicenter Phase 3 Study of Lomitapide in HoFH

<table>
<thead>
<tr>
<th></th>
<th>Baseline (n=29)</th>
<th>Week 26 (n=23)</th>
<th>Change from baseline (%)</th>
<th>p value†</th>
<th>Week 56 (n=23)</th>
<th>Change from baseline (%)</th>
<th>p value†</th>
<th>Week 78 (n=23)</th>
<th>Change from baseline (%)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>11.1 (3.5)</td>
<td>6.1 (2.9)</td>
<td>-46% (-56 to -35)</td>
<td>&lt;0.0001</td>
<td>7.1 (3.7)</td>
<td>-39% (-51 to -27)</td>
<td>&lt;0.0001</td>
<td>7.3 (3.9)</td>
<td>-35% (-48 to -22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>8.7 (2.9)</td>
<td>4.3 (2.5)</td>
<td>-50% (-62 to -39)</td>
<td>&lt;0.0001</td>
<td>5.1 (3.2)</td>
<td>-44% (-57 to -31)</td>
<td>&lt;0.0001</td>
<td>5.4 (3.4)</td>
<td>-38% (-52 to -24)</td>
<td>0.0001</td>
</tr>
<tr>
<td>VLDL cholesterol, mmol/L</td>
<td>0.3 (0.3)</td>
<td>0.3 (0.2)</td>
<td>-45% (-51 to -39)</td>
<td>&lt;0.0001</td>
<td>0.4 (0.4)</td>
<td>-28% (-48 to -10)</td>
<td>0.0185</td>
<td>0.4 (0.4)</td>
<td>-31% (-54 to -7)</td>
<td>0.0389</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mmol/L</td>
<td>10.0 (3.4)</td>
<td>5.1 (2.8)</td>
<td>-50% (-61 to -39)</td>
<td>&lt;0.0001</td>
<td>5.9 (3.6)</td>
<td>-44% (-57 to -31)</td>
<td>&lt;0.0001</td>
<td>6.2 (3.8)</td>
<td>-39% (-53 to -25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.0 (0.4 to 2.9)</td>
<td>0.5 (0.1 to 1.7)</td>
<td>-45% (-61 to -29)</td>
<td>&lt;0.0001</td>
<td>0.7 (0.2 to 2.9)</td>
<td>-29% (-47 to -11)</td>
<td>0.0157</td>
<td>0.7 (0.2 to 4.1)</td>
<td>-31% (-54 to -8)</td>
<td>0.0368</td>
</tr>
<tr>
<td>ApoB, g/L</td>
<td>2.6 (0.8)</td>
<td>1.3 (0.7)</td>
<td>-49% (-60 to -38)</td>
<td>&lt;0.0001</td>
<td>1.3 (0.6)</td>
<td>-45% (-57 to -33)</td>
<td>&lt;0.0001</td>
<td>1.5 (0.8)</td>
<td>-42% (-56 to -29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lipoprotein (a), μmol/L</td>
<td>2.4 (0.6 to 2.1)</td>
<td>1.7 (0.3 to 0.7)</td>
<td>-15% (-38 to 0.8)</td>
<td>0.0003</td>
<td>2.0 (0.5 to 0.6)</td>
<td>-15% (-31 to 0)</td>
<td>0.0111</td>
<td>2.0 (0.6 to 0.6)</td>
<td>-1% (-17 to 6)</td>
<td>0.5827</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.1 (0.3)</td>
<td>1.0 (0.4)</td>
<td>-12% (-20 to 4)</td>
<td>0.0001</td>
<td>1.2 (0.4)</td>
<td>1% (-11 to 13)</td>
<td>0.954</td>
<td>1.1 (0.3)</td>
<td>-5% (-13 to 3)</td>
<td>0.1396</td>
</tr>
<tr>
<td>ApoA-I, g/L</td>
<td>1.2 (0.3)</td>
<td>1.0 (0.2)</td>
<td>-19% (-27 to -4)</td>
<td>0.0003</td>
<td>1.1 (0.3)</td>
<td>1% (-11 to 13)</td>
<td>0.508</td>
<td>1.1 (0.3)</td>
<td>-4% (-10 to 3)</td>
<td>0.1155</td>
</tr>
</tbody>
</table>

Data are mean (SD), median (range) for triglycerides and lipoprotein (a) at baseline, weeks 26, 56, and 78, or mean (95% CI) for percent change. †p values from mixed model. ‡p values from one-sample t test.

*Table: Lipid and lipoprotein concentrations at baseline and weeks 26, 56, and 78 (end of study)*
Single-arm, open label multicenter Phase 3 Study of Lomitapide in HoFH

- Compliance: 93% during efficacy phase, 95% during safety phase
- Among 23 completers
  - 1 @ 5 mg
  - 5 @ 20 mg
  - 6 @ 40 mg
  - 11 @ 60 mg
- Apheresis patients
  - 3 patients permanently discontinued treatment
  - 3 patients increased intervals between treatments
- No clinically meaningful changes in fat soluble vitamins or essential fatty acids

Lancet 2013;381:40-46
Single-arm, open label multicenter Phase 3 Study of lomitapide in HoFH

- Most patients had at least one AE
  - 27 of 29 in efficacy phase, 21 of 23 in safety phase (most mild to moderate)
  - GI symptoms were most common side effect (93%)
    - 3 discontinuations due to GI side effects occurred during titration phase

- 3 of 29 had serious AE (assessed as unrelated or unlikely due to study drug)
  - ACS/angina/respiratory tract infection
  - Elective hysterectomy
  - Chest pain

Lancet 2013;381:40-46
Figure 2: Alanine transaminase and aspartate transaminase levels and percentage of hepatic fat in the liver
Data are mean, 95% CI. Laboratory reference ranges for alanine transaminase levels were 10–40 U/L in men and 10–33 U/L in women; reference ranges for aspartate transaminase levels were 10–43 U/L in men and 10–36 U/L in women (A). Percentage of fat in the liver, as measured by nuclear magnetic resonance spectroscopy at baseline and 26, 56, and 78 weeks of lomitapide treatment (n=20; B).
Single-arm, open label multicenter Phase 3 Study of lomitapide in HoFH

- No patient permanently discontinued therapy due to LFTs
  - 3 of 4 reported consuming quantity of alcohol higher than allowed per protocol
  - No elevations of total bilirubin, alkaline phosphatase
  - 10 patients has LFT increase >3X ULN at least once during the study
  - 4 patients had LFT increases of >5X ULN, resolved with dose reduction or temporary interruption of therapy
  - Doses of 10, 20, 40, and 60 mg

- 6 patients discontinued therapy
  - 2 @ 5 mg, 2 @ 10 mg, 1 @ 20 mg, 1 @ 40 mg
  - 5 patients (17%) discontinued due to adverse events

Lancet 2013;381:40-46
Phase 3 Long-Term Extension Study

Sustained LDL-C lowering and stable hepatic fat levels in patients with homozygous familial hypercholesterolemia treated with the microsomal triglyceride transfer protein inhibitor, lomitapide: results of an ongoing long-term extension study


Phase 3 Long-Term Extension Study - Overview

- Following the 78-week pivotal phase 3 study, 19 of 23 eligible patients entered the long-term extension study
  - Continued lomitapide at their maximum tolerated dose determined in the phase 3 pivotal study, in combination with their usual lipid-lowering therapy (LLT)

- Primary efficacy endpoint mean % change in LDL-C from baseline of the pivotal phase 3 to Week 126 (~2.5 years of treatment).

- Patients remained on concomitant LLT, including oral medications and apheresis, which could be modified at the investigator’s discretion.

- The study is currently ongoing.

Mean percent change from baseline in LDL-C by study visit (Week 126 completers population)


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**Observed changes in LDL-C and other Atherogenic Lipoproteins (n=17, Week 126 completers)**

<table>
<thead>
<tr>
<th>Parameter (mg/dL)</th>
<th>Mean change at Week 26, % (SD)</th>
<th>Mean change at Week 78, % (SD)</th>
<th>Mean change at Week 126, % (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>−55.7 (21.3)</td>
<td>−50.8 (19.8)</td>
<td>−45.5 (31.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC</td>
<td>−49.8 (19.9)</td>
<td>−46.2 (18.8)</td>
<td>−43.2 (25.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VLDL-C</td>
<td>−45.4 (30.0)</td>
<td>−44.2 (34.4)</td>
<td>−36.8 (43.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>−54.7 (20.3)</td>
<td>−51.0 (19.3)</td>
<td>−47.1 (27.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides†</td>
<td>−49.0 (−86.5, 17.3)</td>
<td>−65.1 (−76.1, 21.8)</td>
<td>−53.1 (−83.5, 40.4)</td>
<td>–</td>
</tr>
<tr>
<td>Apo B</td>
<td>−54.1 (21.5)</td>
<td>−54.9 (17.0)</td>
<td>−53.6 (23.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C</td>
<td>−8.5 (17.2)</td>
<td>−5.6 (20.2)</td>
<td>−8.3 (19.3)</td>
<td>0.010</td>
</tr>
<tr>
<td>Apo AI</td>
<td>−8.3 (14.3)</td>
<td>−4.4 (15.3)</td>
<td>−14 (17.7)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

*All comparisons were made versus baseline values at the start of treatment in the pivotal Phase 3 study using a mixed model repeated measures analysis; Data are mean (SD) with the exception of triglycerides†, which are median values with range; Mean (SD) values for triglycerides at Weeks 26, 78, and 126 were: −44.9 (30.2), −44.7 (33.9), and −37.5 [(42.5); p=0.005]
Long-Term Extension Study: Summary of Efficacy Results

- LDL-C levels were statistically significantly reduced from 356 ± 127mg/dL at baseline to 189 ± 120mg/dL (p<0.001).

- LDL-C of ≤100 mg/dL and ≤70 mg/dL was achieved at any time by 13 (68%) and 9 (47%) of 19 patients, respectively.
  - One patient reached <70 mg/dL for the first time in the extension phase.

- One patient discontinued apheresis during the long-term extension.

**Hepatic Safety: Hepatic Fat (N=19 safety population)**

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>N</th>
<th>Median, %</th>
<th>Mean, %</th>
<th>Range, %</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.7</td>
<td>0.8</td>
<td>0, 2.4</td>
</tr>
<tr>
<td>17</td>
<td>17</td>
<td>17</td>
<td>5.9</td>
<td>6.5</td>
<td>1.1–16.3</td>
</tr>
<tr>
<td>126</td>
<td>78</td>
<td></td>
<td>7.6</td>
<td>7.3</td>
<td>0.6–19.0</td>
</tr>
<tr>
<td>12</td>
<td>13</td>
<td>17</td>
<td>7.7</td>
<td>7.9</td>
<td>1.6–24.7</td>
</tr>
<tr>
<td>150</td>
<td>174</td>
<td>17</td>
<td>7.6</td>
<td>10.2</td>
<td>0.7–35.2</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>17</td>
<td>7.6</td>
<td>11.1</td>
<td>0.6–15.6</td>
</tr>
</tbody>
</table>

*NMRS was not performed in two patients due to contraindications. Values represent median ± interquartile range (IQR).

Long-term Extension Study
Conclusions

• Results of the on-going long-term extension study of lomitapide in patients with HoFH are consistent with those observed in the pivotal phase 3 study.

• Lipid lowering efficacy was maintained throughout the study.

• No new safety signals were identified.

• LDL-C percent change from baseline at Week 126 was –45.5%, consistent with the results observed in the phase 3 study.

• AEs were generally manageable and the profile of AEs observed was consistent with those observed in the pivotal study.¹

• Median hepatic fat levels were 6.5% at entry to the long-term extension study and remained stable over the observed study period.

Drug Interactions with Lomitapide

- Weak inhibitor of CYP3A4

- Two prospective open-label studies (130 healthy volunteers)
  - Study 1: 8 open-label treatment arms (probe + lomitapide)
    - Atorvastatin 20 mg + lomitapide 10 mg or 60 mg (CYP3A4)
    - Simvastatin 20 mg + lomitapide 10 mg (CYP3A4)
    - Rosuvastatin 20 mg + lomitapide 20 mg or 60 mg (excreted unchanged in feces)
    - Fenofibrate 145 mg + lomitapide 10 mg (prodrug, hydrolyzed to fenofibric acid, and glucuronide conjugate, eliminated in urine)
    - Ezetimibe 10 mg + lomitapide 10 mg (glucuronide conjugation, fecal excretion)
    - ER niacin 1g + lomitapide 10 mg
  - Study 2
    - Ninth additional group: simvastatin 40 mg + lomitapide 60 mg

Pharmacotherapy. 2013; doi: 10.1002/phar.1351
Drug Interactions with Lomitapide

- **Atorvastatin**
  - Lomitapide 10 mg: no appreciable increase in statin exposure
  - Lomitapide 60 mg: modest dose-dependent effect

- **Simvastatin**
  - More pronounced effect of lomitapide inhibition
  - Significant dose-dependent effect

- **Rosuvastatin**
  - Mainly excreted in the feces
  - Lomitapide 10 mg: no effect on AUC of rosvastatin
  - Lomitapide 60 mg: small effect

- No clinically relevant effects of lomitapide on exposure to fenofibrate, ezetimibe, or ER niacin
Lomitapide

- “Orphan Drug”: available for patients with rare genetic diseases
- Available through a REMS (Risk Evaluation and Mitigation Strategy) program
  - To educate providers about risk of hepatic toxicity and need for careful monitoring
  - To restrict access to patients with homozygous familial hypercholesterolemia
- Prescriber training and certification
- Controlled distribution through certified pharmacies
- Prescription authorization forms
Lomitapide

**Black Box Warning:**

- Can cause elevations in transaminases. In the Pivotal Phase 3 clinical trial, 10 (34%) of the 29 patients treated with lomitapide had at least one elevation in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥3x upper limit of normal (ULN). There were no concomitant clinically meaningful elevations of total bilirubin, international normalized ratio (INR), or alkaline phosphatase.

- Lomitapide also increases hepatic fat, with or without concomitant increases in transaminases. The median absolute increase in hepatic fat was 6% after both 26 and 78 weeks of treatment, from 1% at baseline, measured by magnetic resonance spectroscopy. Hepatic steatosis associated with lomitapide treatment may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis.

- Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and AST regularly as recommended. During treatment, adjust the dose if the ALT or AST are ≥3x ULN. Discontinue lomitapide for clinically significant liver toxicity.

- Because of the risk of hepatotoxicity, lomitapide is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS)
Conclusions
Conclusions

- MTP is a key protein in the assembly and secretion of apoB-containing lipoproteins.
- Mutations in the gene encoding MTP are the molecular basis of abetalipoproteinemia, rare disorder with absence of apoB-containing lipoproteins of intestinal and hepatic origin.
- MTP inhibition with lomitapide significantly reduces LDL-C (~50%) and other apoB-containing lipoproteins.
- Indicated for treatment of HoFH
- Predictable mechanism-based GI side effects, increase in transaminases and increase in hepatic fat of uncertain significance.
- Requires monitoring of LFTs
- Drug-drug interactions possible with moderate and strong CYP3A4 inhibitors (limit dose of simvastatin and lovastatin)
Conclusions

- Dose titration schedule can limit GI side effects
- Due to its mechanism of action it may reduce absorption of fat-soluble vitamins
- Patients are provided with supplements of vit E 400 IU, linoleic acid 200 mg, ALA 210 mg, EPA 110 mg, DHA 80 mg
- Counsel patient in low-fat (<20% energy from total fat) to minimize GI side effects
- Dosed in the evening 2 hours after meal with water—do not take with food
- Limit alcohol to one serving daily
Conclusions

- Inhibitors of CYP3A4 may increase exposure to lomitapide
- Do not exceed 30 mg in patients on weak CYP3A4 inhibitors
  - Use only low-dose simvastatin and lovastatin
- Monitor LFTs: reduce or withhold therapy for significant elevations of transaminases
- Lomitapide increases plasma concentrations of warfarin
  - Monitor INR, particularly after change in lomitapide dose
- Available through REMS program: prescribers must be educated and certified on knowledge of liver-related side effects
- Patient support program available: COMPASS
Case Study: BA

- February 2013: on rosuvastatin 40 mg, EZE 10 mg, colesevalam 3.75 g
  - Pre-apheresis LDL-C 145-178 mg/dl
  - Initiated therapy with lomitapide
  - Did well on 5 mg daily, developed nausea when increased to 10 mg daily
  - Reduced to 10 mg QOD
Case Study: BA

- September, 2013: rosuvastatin 40 mg, EZE 10 mg, colesevalam 3.75 g, lomitapide 10 mg QOD
  - Gradually reduced frequency of LDL apheresis
  - Last treatment after 6 weeks: pre-Rx LDL-C 45 mg/dl, post-Rx LDL-C 2 mg/dl
  - Discontinued LDL apheresis
  - Most recent LDL-C 65 mg/dl