FDA Introductory Remarks

Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) Meeting

May 10, 2018

John Sharretts, M.D.
Familial Chylomicronemia Syndrome (FCS)

- Rare, autosomal recessive disease
- Inability to process dietary fats
- Very low lipoprotein lipase (LPL) activity
- Accumulation of chylomicron particles
- Elevated plasma triglyceride (TG) levels

Chylomicron

Apo E

Apo B-48

Apo C-II

Apo C-III

Apo A

Cholesterol

TG (>85%)
FCS Clinical Features

- Childhood onset
- Very severe hypertriglyceridemia
- Recurrent acute pancreatitis
- Episodic abdominal pain

- Lipemia retinalis (above right)
- Eruptive cutaneous xanthomas (left)
- Hepatosplenomegaly

Volanesorsen

• Anti-sense oligonucleotide (ASO)
• Inhibits translation of Apo C-III

- Decreased APO C-III levels
- Increased triglyceride (TG) clearance
- Decreased TG levels
Benefit/Risk Assessment

Surrogate endpoints:
• Triglycerides

Potential clinical benefits:
• Pancreatitis
• Abdominal pain
• Other symptoms important to FCS patients

Identified risks:
• Thrombocytopenia
• Bleeding
• Injection-site reactions
• Hypersensitivity and Immune reactions

Potential risks:
• Severe bleeding
• Renal toxicity
• Liver toxicity
<table>
<thead>
<tr>
<th>Section</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Review Introduction</td>
<td>Mary D. Roberts, MD</td>
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<tr>
<td>Statistical Review of Efficacy</td>
<td>Alexander Cambon, PhD</td>
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<tr>
<td>Clinical Review</td>
<td>Mary D. Roberts, MD</td>
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<tr>
<td>Clinical Pharmacology Review</td>
<td>Yunzhao Ren, MD, PhD</td>
</tr>
<tr>
<td>Risk Evaluation and Mitigation Strategy (REMS)</td>
<td>Ingrid N. Chapman, PharmD, BCPS</td>
</tr>
<tr>
<td>Considerations</td>
<td></td>
</tr>
<tr>
<td>Benefit/Risk Summary</td>
<td>Mary D. Roberts, MD</td>
</tr>
</tbody>
</table>
Clinical Review Introduction

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

May 10, 2018

Mary Dunne Roberts, MD
Outline

• Familial Chylomicronemia Syndrome (FCS)
• Regulatory history
• Study population
• Efficacy – Alexander Cambon, PhD
• Safety
• Risk management
  – Dosing regimen – Yunzhao Ren, MD, PhD
  – Risk Evaluation and Mitigation Strategy – Ingrid Chapman, PharmD
• Summary
Familial Chylomicronemia Syndrome

- Rare, autosomal recessive disease, caused by biallelic pathogenic mutations in the lipoprotein lipase (LPL) gene or its co-factors
- Absent or reduced LPL → defective processing of TG from chylomicrons → persistently elevated TG
- Prevalence 1 to 2 per million individuals

<table>
<thead>
<tr>
<th>Gene</th>
<th>Function</th>
<th>Percent of monogenic mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPL</td>
<td>TG hydrolysis and peripheral uptake of free fatty acids</td>
<td>95</td>
</tr>
<tr>
<td>Apo C-II</td>
<td>Required co-factor of LPL</td>
<td>2</td>
</tr>
<tr>
<td>GPIHBP1</td>
<td>Stabilizes binding of chylomicrons</td>
<td>2</td>
</tr>
<tr>
<td>apoA-V</td>
<td>Enhances LPL activity</td>
<td>0.6</td>
</tr>
<tr>
<td>LMF-1</td>
<td>Chaperone molecule required for proper LPL folding and/or expression</td>
<td>0.4</td>
</tr>
</tbody>
</table>

apoC-II: apolipoprotein C-II; GPIHBP1: glycosylphosphatidylinositol-anchored high density lipoprotein-binding protein 1; apoA-V: apolipoprotein A-V; LMF1: lipase maturation factor 1
Source: Brahm & Hegle 2015
FCS: Signs & Symptoms

• Typical onset of symptoms in childhood or adolescence
• Most serious consequence – pancreatitis
• Recurrent abdominal pain
• Lipemic blood, eruptive xanthomas, lipemia retinalis hepatosplenomegaly
• Other reported symptoms include fatigue, forgetfulness, depression
Current Treatment Options

• Dietary intervention mainstay of treatment
  – Strict low fat diet (20 grams of fat)

• Medications to lower TG (fibrates, niacin) ineffective

• No currently FDA approved therapies
Applicant Criteria for FCS Diagnosis

A specific diagnosis of FCS can be made by the following clinical criteria:

1. Fasting TG levels >750 mg/dL that are refractory to standard lipid lowering therapy

   AND

2. At least one of the following:
   • History of acute pancreatitis; OR
   • History of childhood pancreatitis; OR
   • History of recurrent abdominal pain without other explainable cause; OR
   • Family history of hypertriglyceridemia

   AND

3. Persistent chylomicronemia after exclusion of contributing factors

Additional supportive clinical findings include eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly.

“Genetic testing can be used for additional information, but a negative genetic test is not exclusionary of FCS.”
Diagnosis of FCS

Diagnostic algorithm for FCS
-Stroes E. Athero Suppl 2017

• “Once the patient is considered possibly affected by LPLD, a fundamental step to establish a correct diagnosis is genetic analysis.”

Familial Lipoprotein Lipase Deficiency
[Updated 2017 Jun 22]. GeneReviews®

• “The majority of individuals with chylomicronemia and plasma triglyceride concentration greater than 2000 mg/dL do not have Familial LPL deficiency”

LPLD: Lipoprotein lipase deficiency
## End of Phase 2 Meeting

<table>
<thead>
<tr>
<th>Topic</th>
<th>FDA Recommendations</th>
<th>Phase 3 Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient population</td>
<td>• Include patients with history of pancreatitis&lt;br&gt;• Do not exclude patients with low platelets&lt;br&gt;• Discuss future plans for pediatric patients</td>
<td>• Enriched for patients with pancreatitis&lt;br&gt;• No platelet exclusion criterion</td>
</tr>
<tr>
<td>Endpoint</td>
<td>• Add endpoints clinically meaningful to patients living with FCS</td>
<td>• Patient-reported abdominal pain&lt;br&gt;• Quality of Life questionnaires&lt;br&gt;• Pancreatitis events adjudicated</td>
</tr>
<tr>
<td>Safety Database</td>
<td>• Increase safety database</td>
<td>• Increased to 1 year placebo-controlled pivotal trial&lt;br&gt;• 6-month trial in patients with HTG</td>
</tr>
<tr>
<td>Dose</td>
<td>• Consider additional dose exploration</td>
<td>• 300 mg/week</td>
</tr>
</tbody>
</table>

HTG: hypertriglyceridemia
# Phase 3 Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Inclusion Criteria (selected)</th>
</tr>
</thead>
</table>
| CS6-pivotal   | Randomized (R), double-blind (DB), placebo-controlled (PC), 52-week 66 patients, 1:1 300 mg/week | - History of chylomicronemia (lipemic blood or fasting TG ≥880 mg/dL)  
- Screening TG ≥ 750 mg/dL  
- Documentation of genetics consistent with Type I hyperlipoproteinemia  
  - LPL, ApoC-II, GPIHBP1, Apo A-V, LMF-1  
- OR  
  - Documentation of low LPL activity <20% of normal  
- History of pancreatitis (28% cap for patients with no pancreatitis) |
| CS16-HTG      | R, DB, PC 26-week 113 patients, 2:1 300 mg/week Amended to 300 mg QOW at Week 13 | - Screening TG ≥ 500 mg/dL  
- FCS patients allowed to enroll (by amendment) total 7 patients |
| CS7-OLE (ongoing) | Open-label, 104 week 70 patients (planned) 300 mg/week | - Patients with FCS completed CS6-pivotal or CS16-HTG  
- Newly identified patients with FCS (same criteria as CS6-pivotal) |

QOW: Every other week  
OLE: Open-label extension
# Study Population

<table>
<thead>
<tr>
<th></th>
<th>CS6-pivotal</th>
<th>CS16-HTG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>Male</td>
<td>46%</td>
<td>76%</td>
</tr>
<tr>
<td>White</td>
<td>80%</td>
<td>93%</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>TG median (Q1, Q3) mg/dL</td>
<td>1985 (1179, 3047)</td>
<td>884 (655, 1587)</td>
</tr>
<tr>
<td>LDL-C mg/dL</td>
<td>28</td>
<td>61</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>76%</td>
<td>29%</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>15%</td>
<td>35%</td>
</tr>
<tr>
<td>Thrombocytopenia (by history)</td>
<td>5%</td>
<td>0</td>
</tr>
<tr>
<td>Fibrate</td>
<td>49%</td>
<td>40%</td>
</tr>
<tr>
<td>Statin</td>
<td>20%</td>
<td>52%</td>
</tr>
<tr>
<td>Platelet aggregation inhibitors (excluding heparin)</td>
<td>20%</td>
<td>36%</td>
</tr>
</tbody>
</table>
Baseline Abdominal Pain – CS6-pivotal

• Disease Symptom Diary completed weekly during screening period (6 to 8 weeks)
  – Did you have abdominal pain related to your disease during the past week? Yes/No
  – Numeric rating score (0 to 10)
• During the 6 week screening period
  – 74% of patients did not report any abdominal pain
  – Only 17 (26%) reported abdominal pain
    • 6 patients rated abdominal pain score ≥ 7
CS6-pivotal: Challenges in Diagnosis

• 9 of 66 patients with TG ≥ 750 mg/dL with no confirmatory on-study testing consistent with FCS
  – 3 patients enrolled based on initial genetic assessment
    • on-study geneticist did not confirm pathogenic mutations
  – 6 patients enrolled based on LPL activity testing¹
    • Initial lab result not confirmed in reference lab (n=5)
    • Not done (n=1)

¹ By medical history or initial on-study testing
Volanesorsen: Efficacy Evaluation
Efficacy Endpoints

• Primary source for efficacy – CS6-pivotal
• Primary Endpoint: Change in TG at Month 3
• Other Endpoints of Interest
  – Abdominal Pain – Patient Reported Outcome
  – Quality of Life Questionnaires
  – Pancreatitis
Statistical Review of Efficacy

NDA 210645

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

May 10, 2018

Alexander Cambon, PhD, Statistical Reviewer
Outline

• Brief Overview of Primary and Secondary Endpoints
• Treatment Discontinuation and Missing Triglyceride (TG) Data
• TG Results
• Select Secondary Endpoint Results
• Select Exploratory and Post-Hoc Results
• Issues and Conclusions
Primary and Secondary Endpoints

• Primary Endpoint - Percent Change in Fasting TG at 3 Months
• Secondary Endpoints
  • Fasting TG < 750 mg/dL at 3 Months
  • Percent Change from Baseline in Fasting TG at 6 and 12 Months
  • Average of Maximum Intensity of Patient Reported Abdominal Pain During the Treatment Period
  • Percent Change from Baseline in Postprandial TG Area Under the Curve
  • At Least 40% Reduction in Fasting TG at 3 Months
  • Change from Baseline in Fasting TG at 3, 6, and 12 Months
  • Frequency of Composite Episodes of Acute Pancreatitis and Patient Reported Abdominal Pain During the On-Treatment Period
  • Change from Baseline in Hepatic Volume

These Endpoints Above Were the Only Ones Included In The Multiple Testing Hierarchy to Control Type I Error
Greater Treatment Discontinuation on Volanesorsen

![Graph showing treatment discontinuation](Image)
## Treatment Discontinuation and Missing TG Data

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=33)</th>
<th>Volanesorsen (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinued Treatment by 3 Months</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Missing TG Data at 3 Months</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Discontinued Treatment by 12 Months</td>
<td>1 (3%)</td>
<td>15 (45%)</td>
</tr>
<tr>
<td>Missing TG Data at 12 Months</td>
<td>1 (3%)</td>
<td>6 (18%)</td>
</tr>
</tbody>
</table>
Percent Change in TG Results

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo</th>
<th>Volanesorsen</th>
<th>Difference (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (Adjusted Mean)</td>
<td>n (Adjusted Mean)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>18</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>31</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>12</td>
<td>27</td>
</tr>
</tbody>
</table>

*Washout imputation used for missing data

There was a large and statistically significant effect on the primary endpoint of percent change in TG at 3 months.
Cumulative Distribution Functions of Percent Change in TG at 3 Months
### Percent Change in TG Results

<table>
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<th>Difference (95% confidence interval)</th>
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<tbody>
<tr>
<td></td>
<td>n Adjusted Mean</td>
<td>n Adjusted Mean</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>33 18</td>
<td>33 -77</td>
<td>-94 (-122, -67)</td>
</tr>
<tr>
<td>6</td>
<td>31 24</td>
<td>29 -48</td>
<td>-72 (-95, -49)*</td>
</tr>
<tr>
<td>12</td>
<td>32 12</td>
<td>27 -33</td>
<td>-45 (-70, -19)*</td>
</tr>
</tbody>
</table>

*FDA analysis with washout imputation for missing data

Some attenuation in the average effect in all patients can be seen at 6 months
Percent Change in TG Results

<table>
<thead>
<tr>
<th>Month</th>
<th>Placebo n</th>
<th>Placebo Adjusted Mean</th>
<th>Volanesorsen n</th>
<th>Volanesorsen Adjusted Mean</th>
<th>Difference (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>33</td>
<td>18</td>
<td>33</td>
<td>-77</td>
<td>-94 (-122, -67)</td>
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<tr>
<td>6</td>
<td>31</td>
<td>24</td>
<td>29</td>
<td>-48</td>
<td>-72 (-95, -49)*</td>
</tr>
<tr>
<td>12</td>
<td>32</td>
<td>12</td>
<td>27</td>
<td>-33</td>
<td>-45 (-70, -19)*</td>
</tr>
</tbody>
</table>

*FDA analysis with washout imputation for missing data

Some further attenuation in the average effect in all patients can be seen at 12 months
### Proportion of Patients with TG Less Than Select Thresholds at 3 and 12* Months

<table>
<thead>
<tr>
<th>TG Threshold (mg/dL)</th>
<th>Month</th>
<th>Placebo (N=33)</th>
<th>Volanesorsen (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 500</td>
<td>3</td>
<td>0 (0%)</td>
<td>18 (55%)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1 (3%)</td>
<td>10 (30%)</td>
</tr>
<tr>
<td>&lt; 1000</td>
<td>3</td>
<td>5 (15%)</td>
<td>27 (82%)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>6 (18%)</td>
<td>14 (42%)</td>
</tr>
<tr>
<td>&lt; 2000</td>
<td>3</td>
<td>14 (42%)</td>
<td>32 (97%)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>14 (42%)</td>
<td>22 (67%)</td>
</tr>
</tbody>
</table>

Cell contents are number (percent) of randomized patients achieving that threshold
*12-month analyses impute subjects with missing data as non-responders, i.e., as having a TG value ≥ threshold
Abbreviations: mg/dL – milligrams per deciliter
Nominal p-values <0.01 for all analyses, based on logistic regression adjusting for log baseline TG and the two stratification factors: history of pancreatitis, and concurrent omega-3 fatty acids and/or fibrates
Primary and Secondary Endpoints

- Primary Endpoint - Percent Change in Fasting Triglycerides (TG) at 3 Months
- Secondary Endpoints
  - Fasting TG < 750 mg/dL at 3 Months
  - Percent Change from Baseline in Fasting TG at 6 and 12 Months
  - Average of Maximum Intensity of Patient Reported Abdominal Pain During the Treatment Period
  - Percent Change from Baseline in Postprandial TG AUC
  - At Least 40% Reduction in Fasting TG at 3 Months
  - Change from Baseline in Fasting TG at 3, 6, and 12 Months
  - Frequency of Composite Episodes of Acute Pancreatitis and Patient Reported Abdominal Pain During the On-Treatment Period
  - Change from Baseline in Hepatic Volume
Average Maximum Intensity of Patient Reported Abdominal Pain

• Each week, patients asked if they had abdominal pain in previous week
• If yes, patients asked to report maximum pain intensity during previous week on 0-10 numerical rating scale (right)
• Weekly maximum pain intensity values averaged within patient over on-treatment period

Source - Applicant
Frequency of Composite of Acute Pancreatitis and Abdominal Pain

• Event definition:
  – A weekly maximum intensity abdominal pain score of at least 4
    OR
  – An adjudicated acute pancreatitis event

• Yearly rate of composite endpoint derived for on-treatment period
Proportion of Subjects with Missing Abdominal Pain Measurements Over Time

Source - Applicant
Select Secondary Endpoint Results – Abdominal Pain and Acute Pancreatitis

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Volanesorsen</th>
<th>Difference (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Maximum Weekly Abdominal Pain over Treatment Period (0-10 Scale)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>33</td>
<td>0.36</td>
<td>Volanesorsen</td>
</tr>
<tr>
<td><strong>Rate of Composite Episodes of Acute Pancreatitis or Abdominal Pain ≥4 (Events Per Patient-Year)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>33</td>
<td>2.04</td>
<td>Volanesorsen</td>
</tr>
</tbody>
</table>

* 13 (39%) and 12 (36%) patients had at least one event on placebo and volanesorsen, respectively
## Additional Exploratory Abdominal Pain Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (n=33)</th>
<th>Volanesorsen (n=33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (Percent) of Patients with Any Abdominal Pain During Treatment Period</td>
<td>14 (42%)</td>
<td>15 (45%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Worst Maximum Weekly Abdominal Pain over Treatment Period (0-10 scale)</td>
<td>2.70</td>
<td>2.33</td>
<td>0.65</td>
</tr>
</tbody>
</table>


### Additional Exploratory Pancreatitis Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (n=33)</th>
<th>Volanesorsen (n=33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (Percent) Who Had an Attack During Treatment Period</td>
<td>3 (9%)</td>
<td>1 (3%)</td>
<td>0.61</td>
</tr>
<tr>
<td>Rate of Adjudicated Pancreatitis During On-Treatment Period (Events Per Patient-Year)</td>
<td>0.11</td>
<td>0.09</td>
<td>0.84</td>
</tr>
</tbody>
</table>
Limitations of Analyses of Abdominal Pain and Pancreatitis

- Limited abdominal pain before and during study
  - 74% did not report abdominal pain during 6-week screening period
  - 56% did not report abdominal pain during treatment period
    - Majority of reported abdominal pain was mild/moderate
- Very few pancreatitis events
  - Only 4 patients with events (5 total events)

⇒ Study likely not powered to detect effects on these outcomes
⇒ While study does not provide evidence of effects, it also does not rule out meaningful effects
### Select SF-36 Domain Change from Baseline Results at Month 3 and Month 12

<table>
<thead>
<tr>
<th>Domain (0-100 scale)</th>
<th>Month</th>
<th>Placebo</th>
<th>Volanesorsen</th>
<th>Difference (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>n</td>
<td>Adjusted Mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>3</td>
<td>25</td>
<td>24</td>
<td>-1.50</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>18</td>
<td>24</td>
<td>-1.28</td>
</tr>
<tr>
<td>Vitality</td>
<td>3</td>
<td>25</td>
<td>24</td>
<td>-0.32</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>18</td>
<td>15</td>
<td>0.22</td>
</tr>
<tr>
<td>Bodily Pain</td>
<td>3</td>
<td>25</td>
<td>24</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>18</td>
<td>15</td>
<td>1.47</td>
</tr>
<tr>
<td>Physical Role Functioning</td>
<td>3</td>
<td>25</td>
<td>24</td>
<td>-0.94</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>18</td>
<td>15</td>
<td>-2.03</td>
</tr>
</tbody>
</table>
Subgroup Analyses Emphasized by Applicant

- Analyses within subgroups defined by abdominal pain during screening and Week 1
- Analyses within subgroups defined by history of pancreatitis
Subgroup Analyses Selected from Huge Number of Analyses Conducted

• Primary and secondary endpoints
  – Pre-specified, included in multiple testing hierarchy

• >100 tertiary/exploratory endpoints and analyses
  – Pre-specified but not in multiple testing hierarchy
  – e.g., worst abdominal pain, proportion/rate of pancreatitis, analyses in subgroup with baseline abdominal pain, SF-36, EQ-5D, etc.

• >100 post-hoc (unplanned) analyses
  – Not pre-specified; found only in the Clinical Study Report or Synopsis
  – e.g., analyses of many endpoints in subgroup with pancreatitis history, analyses with “zero” imputation, etc.
Select Unplanned Subgroup Analyses for Acute Pancreatitis

<table>
<thead>
<tr>
<th>Subjects with At Least One Prior Event</th>
<th>Placebo</th>
<th>Volanesorsen</th>
<th>Nominal P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Had Attack During Treatment Period</td>
<td>10</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
<td>0.07</td>
</tr>
<tr>
<td>Subjects with At Least Two Prior Events</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Had Attack During Treatment Period</td>
<td>3</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Subjects with No Prior Events</td>
<td>23</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Had Attack During Treatment Period</td>
<td>0</td>
<td>1</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Fisher’s exact test
Select Unplanned Subgroup Analyses for Acute Pancreatitis

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Volanesorsen</th>
<th>Nominal P-Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with At Least One Prior Event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had Attack During Treatment Period</td>
<td>10</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
<td>0.07</td>
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<tr>
<td>Subjects with At Least Two Prior Events</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Had Attack During Treatment Period</td>
<td>4</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Subjects with No Prior Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had Attack During Treatment Period</td>
<td>23</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1</td>
<td>0.46</td>
</tr>
</tbody>
</table>

*Fisher’s exact test
Issues and Conclusions About Subgroup Analyses Emphasized by Applicant

• Planned secondary/exploratory analyses of the endpoints in overall population show no evidence of effects
• Selected among hundreds of exploratory/post-hoc analyses
  – Low p-values expected just by chance
• Analyses likely biased toward volanesorsen due to greater treatment discontinuation, missing data
  – Analyses comparing counts/proportions particularly inappropriate

⇒ No convincing evidence of effects
Conclusions

• Large effect on triglycerides at 3 months
• No evidence of benefit with respect to abdominal pain, pancreatitis, or quality of life
  – For rare outcomes such as pancreatitis, number of events likely too small to reliably evaluate whether or not VLN has an effect

⇒ Uncertainty about magnitude of effect on direct measures of how patients function or feel
Clinical Review

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

May 10, 2018

Mary Dunne Roberts, MD
Volanesorsen (VLN): Safety Evaluation

- Safety review approach
- Extent of exposure
- Overview of adverse events, serious adverse events, and discontinuations
- Adverse events of interest
  - Injection site reactions
  - Immunogenicity/Hypersensitivity - Flu-like reactions
  - Renal and hepatic events
  - Thrombocytopenia/Bleeding
Safety Review Approach

Phase 3 trials – main source of safety data

• Primary data for safety review
  – CS6-pivotal

• Supportive data
  – CS16-HTG: placebo vs. all VLN-treated patients
  – CS7-OLE
## Exposure

- **Initial data cut-off (January 18, 2017) for NDA submission**

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Exposure (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VLN (total)</td>
<td>VLN (FCS only)</td>
</tr>
<tr>
<td>CS6-pivotal</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>CS16-HTG</td>
<td>75</td>
<td>5</td>
</tr>
<tr>
<td>CS7-OLE (treatment-naïve)</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>126</strong></td>
<td><strong>56</strong></td>
</tr>
</tbody>
</table>

- **4-month safety update (August 31, 2017)**

<table>
<thead>
<tr>
<th></th>
<th>Number of Patients</th>
<th>Exposure (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VLN (total)</td>
<td>VLN (FCS only)</td>
</tr>
<tr>
<td>CS6-pivotal</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>CS16-HTG</td>
<td>75</td>
<td>5</td>
</tr>
<tr>
<td>CS7-OLE (treatment-naïve)</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>151</strong></td>
<td><strong>81</strong></td>
</tr>
</tbody>
</table>
Disposition of Patients from CS6 through CS7

*As of 4-month safety update
## Overview of Adverse Events

### Phase 3 trials

<table>
<thead>
<tr>
<th></th>
<th>CS6-pivotal</th>
<th>CS16-HTG</th>
<th>CS7-OLE*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>VLN 300 mg</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>N=33</td>
<td>N=33</td>
<td>N=38</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Treatment-emergent adverse event</td>
<td>31 (94)</td>
<td>32 (97)</td>
<td>34 (90)</td>
</tr>
<tr>
<td># events</td>
<td>227</td>
<td>985</td>
<td>194</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>5 (15)</td>
<td>7 (21)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>1 (3)</td>
<td>14 (42)</td>
<td>4 (11)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>0</td>
<td>9 (27)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Voluntary withdrawal</td>
<td>1 (3)</td>
<td>4 (12)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Investigator judgment</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*4-month safety update*
Most Common Adverse Drug Reactions
CS6-pivotal: ≥10% incidence and >placebo, excluding injection site reactions

- Thrombocytopenia
- Arthralgia
- Abdominal pain
- Headache
- Fatigue
- Erythema
- Nausea
- Vomiting
- Diarrhea
- Asthenia
- Myalgia
- Epistaxis
- Petechiae
- Arthralgia
- Pain in extremity
- Diabetes mellitus

Percentage of patients with adverse event
Serious Adverse Events (SAE)

### Phase 3 trials

<table>
<thead>
<tr>
<th></th>
<th>CS6-pivotal</th>
<th>CS16-HTG</th>
<th>CS7-OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=33</td>
<td>VLN 300 mg N=33</td>
<td>Placebo N=38</td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>5 (15)</td>
<td>7 (21)</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>

Notable SAEs in VLN-treated patients

- Thrombocytopenia
- Serum-sickness
- Anaphylaxis
- Myalgia
Discontinuations Due to Adverse Events

CS6-pivotal

• Nine (27%) of VLN-treated vs. no placebo-treated discontinued treatment due to an adverse event (AE)

<table>
<thead>
<tr>
<th>Treatment discontinuation due to AE</th>
<th>VLN 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count decreased</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
</tr>
<tr>
<td>Injection Site Reactions &amp; Fatigue</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
</tr>
<tr>
<td>Hyperhidrosis &amp; Chills</td>
<td>1</td>
</tr>
<tr>
<td>Erythema</td>
<td>1</td>
</tr>
</tbody>
</table>
Safety Concerns

• Injection site reactions
• Immunogenicity/Hypersensitivity – Flu-like reactions
• Renal events
• Hepatic events
• Thrombocytopenia/Bleeding
Safety Concerns

• Injection site reactions
• Immunogenicity/Hypersensitivity - Flu-like reactions
• Renal events
• Hepatic events
• Thrombocytopenia/Bleeding
Injection Site Reactions (ISR)

<table>
<thead>
<tr>
<th></th>
<th>CS6-pivotal</th>
<th>CS16-HTG</th>
<th>CS7-OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection site reactions</td>
<td>Placebo N=33</td>
<td>VLN 300 mg N=33</td>
<td>Placebo N=38</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>0</td>
<td>79%</td>
<td>8%</td>
</tr>
<tr>
<td>Events</td>
<td>0</td>
<td>497</td>
<td>8</td>
</tr>
</tbody>
</table>

- Most common adverse event reported
- Average of 6 injections before ISR event reported (CS6)
- Median time to resolution 8 days (CS6)
- Skin discoloration noted in 20 to 30% of patients
- One patient in pivotal trial discontinued due to ISR (CS6)

www.fda.gov
Injection Site Reactions

- Photo taken 4 months after last VLN administration
- Patient received total of 13 doses of VLN
- Reported AEs at injection site with first dose
- Discoloration, loss of sensitivity, and skin depression not resolved
Safety Concerns

• Injection site reactions
• Immunogenicity/Hypersensitivity - Flu-like reactions
• Renal events
• Hepatic events
• Thrombocytopenia/Bleeding
Immunogenicity

- Patients generally remain positive for anti-VLN antibodies
- No effect observed on TG or platelet count
- Potential association with Anti-VLN antibodies and hypersensitivity events – although small number of events
Hypersensitivity

<table>
<thead>
<tr>
<th></th>
<th>CS6-pivotal</th>
<th>CS16-HTG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=33</td>
<td>Placebo N=38</td>
</tr>
<tr>
<td></td>
<td>VLN 300 mg N=33</td>
<td>VLN 300 mg N=75</td>
</tr>
<tr>
<td>Hypersensitivity events</td>
<td>6 (18%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td></td>
<td>12 (36%)</td>
<td>19 (25%)</td>
</tr>
<tr>
<td>ADA (+)</td>
<td>ADA (-)</td>
<td>ADA (+)</td>
</tr>
<tr>
<td>n=11</td>
<td>n=22</td>
<td>n=12</td>
</tr>
<tr>
<td>5 (45%)</td>
<td>7 (32%)</td>
<td>4 (33%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 (24%)</td>
</tr>
</tbody>
</table>

• Erythema reported by greatest number of patients
  – One FCS patient experienced “erythema extended to whole body surface” after 3 months of VLN treatment; required steroids, antihistamine, and cyclosporine therapy

• Two serious cases of hypersensitivity in non-FCS patients
Hypersensitivity: Serum Sickness

- Serum sickness
- 47-year-old male with HTG
- 300 mg VLN weekly
- 18\textsuperscript{th} dose, next day flu-like symptoms
- 19\textsuperscript{th} dose, flu-like symptoms
- VLN was held
- Flu like symptoms persist
  - muscle aches, fever 102-104F, elevated LFT
- Positive anti-volanesorsen antibody test
  - 19 days after last dose with a titer of 6400
  - Peak 25,600
- Started high dose prednisone
- Rheumatologist diagnosed serum sickness

LFT: Liver function tests
Hypersensitivity: Anaphylaxis

- 40-year-old man with familial partial lipodystrophy
- VLN 300 mg/weekly
- Starting with 17\textsuperscript{th} dose, Patient experienced flu-like symptoms within 12 hours of dosing
- Anaphylactic reaction occurred within 5 minutes of his 25\textsuperscript{th} dose – required emergent treatment (epinephrine)
- Patient had positive anti-VLN antibodies at the time of anaphylactic reaction

[Graph showing titer result over days after randomization with markers for dosing, nausea, vomiting, muscle aches, elevated hsCRP, and other adverse events.]
Flu-like Reactions (FLR)

• Applicant Definition
• Starting on day of injection or next day:
  – Flu-like illness; OR
  – Pyrexia or feeling hot or body temperature increased **PLUS**
    • At least 2 of the following
      - Chills
      - Myalgia
      - Arthralgia

• FDA Definition
• Starting on day of injection or next day:
  – At least 1 of the following
    - Flu-like illness
    - Chills
    - Myalgia
    - Arthralgia
    - Pyrexia
    - Feeling hot
    - Body temperature increased
**Flu-like Reaction**

<table>
<thead>
<tr>
<th></th>
<th>CS6-pivotal</th>
<th>CS16-HTG</th>
<th>CS7-OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo N=33</td>
<td>VLN 300 mg N=33</td>
<td>Placebo N=38</td>
</tr>
<tr>
<td>FLR (Applicant definition)</td>
<td>0</td>
<td>2 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>FLR (FDA definition)</td>
<td>1</td>
<td>9 (27%)</td>
<td>0</td>
</tr>
</tbody>
</table>

- Additional patients with symptoms suggestive of a flu-like reaction observed with VLN-administration using more sensitive definition of a FLR.
Safety Concerns

- Injection site reactions
- Immunogenicity/Hypersensitivity - Flu-like reactions
- Renal events
- Hepatic events
- Thrombocytopenia/Bleeding
Renal Events

• Non-clinical signal for proteinuria in non-human primates
• Few renal-related adverse events in CS6: 4 (12%) VLN vs. 0 placebo
• CS6: 4 VLN vs. 0 placebo had modest increases in creatinine ≥0.3 mg/dL (n=3) or ≥50% (n=1) above baseline
• In CS16, 2 VLN-treated patients met renal-related stopping rules:
  – 1 for worsening proteinuria (baseline 242 mg/day → ~1500 mg/day on 3 separate 24-hr urine collections)
  – 1 for increased creatinine (1.2 mg/dL at baseline → ~2.3 mg/dL at week 8)
• CS16: 12 (16%) VLN vs. 3 (8%) placebo with renal-related adverse events
• No clear evidence for nephrotoxicity, including immune-mediated etiologies, but proteinuria was not well-quantified
Safety Concerns

• Injection site reactions
• Immunogenicity/Hypersensitivity - Flu-like reactions
• Renal events
• Hepatic events
• Thrombocytopenia/Bleeding
### Categorical Liver Enzyme Thresholds

<table>
<thead>
<tr>
<th></th>
<th>CS6-pivotal</th>
<th>CS16-HTG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo VLN</td>
<td>Placebo VLN</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3x ULN</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>&gt;5x ULN</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10x ULN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>AST</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3x ULN</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>&gt;5x ULN</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>&gt;10x ULN</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Bilirubin &gt;2xULN</strong></td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

ULN: upper limit of normal; ALT: alanine transaminase; AST: aspartase transaminase
Hepatic Events

48-year-old women with high TG
- 4 doses VLN
- ALT>8x ULN, AST >10x ULN, Bilirubin normal
- Liver enzymes resolved with treatment discontinuation

Source: Applicant Figure CSR CS16
Hepatic Events

• Small number of VLN-treated patients with elevations in liver transaminases; causal relationship cannot be definitively excluded

• No instances of Hy’s Law observed in VLN-treated patients
Safety Concerns

• Injection site reactions
• Immunogenicity/Hypersensitivity - Flu-like reactions
• Renal events
• Hepatic events
• Thrombocytopenia/Bleeding
## Platelet Monitoring

<table>
<thead>
<tr>
<th></th>
<th>Original Protocol June 2014</th>
<th>Amendment 6/updates May/June 2016</th>
<th>Amendment 7 April 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of routine platelet monitoring</td>
<td>4 to 6 weeks</td>
<td>Every 2 weeks Platelet count and trend reviewed before dosing</td>
<td>Every week</td>
</tr>
<tr>
<td>Permanent discontinuation</td>
<td>Platelet &lt;50K/uL and major or clinically relevant bleeding</td>
<td>Platelet &lt;25K/uL 25 to &lt;75K/uL on QOW dosing or &lt;75K/uL and major or clinically relevant bleeding</td>
<td>Platelet &lt;50K/uL</td>
</tr>
<tr>
<td>Dose rechallenge</td>
<td>Up to 2 times once platelet ≥100K/uL, medical monitor approval</td>
<td>1 rechallenge if patient on weekly dosing, platelet ≥100K/uL, medical monitor approval</td>
<td></td>
</tr>
<tr>
<td>Dose interval</td>
<td></td>
<td>CS6-pivotal: QOW when platelet &lt;100K/uL or with rechallenge</td>
<td></td>
</tr>
</tbody>
</table>
VLN Lowers Platelet Count

- Average 30% reduction over first 6 months with VLN treatment
## Low Nadir Platelet Counts with VLN

<table>
<thead>
<tr>
<th>PLT count (K/uL)</th>
<th>CS6-pivotal</th>
<th>CS16-HTG</th>
<th>CS7-OLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PBO</td>
<td>VLN</td>
<td>PBO</td>
</tr>
<tr>
<td>&lt;140</td>
<td>9 (27%)</td>
<td>25 (76%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>0</td>
<td>18 (55%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>100 to &lt;140</td>
<td>9 (27%)</td>
<td>7 (21%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>75 to &lt;100</td>
<td>0</td>
<td>6 (18%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>50 to &lt;75</td>
<td>0</td>
<td>9 (27%)</td>
<td>0</td>
</tr>
<tr>
<td>25 to &lt;50</td>
<td>0</td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>&lt;25</td>
<td>0</td>
<td>2 (6%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Table does not include 2 additional VLN-treated patients with platelet count <50 K/uL occurring in phase 2 dose-finding study and CS7-OLE after 4-month safety update.
Patients Experienced Severe Thrombocytopenia*

*As of 4-month safety update
34 year old woman with FCS, no history of pancreatitis

Most Recent 15-day Safety Report – Feb 2018
Thrombocytopenia <25K/uL
Platelet Count <25K/uL Occurred with Enhanced Platelet Monitoring and Dose Adjustment

- Change in dosing regimen and weekly platelet monitoring did not prevent Grade 4/life-threatening thrombocytopenia
- Unknown if proposed monitoring/dose adjustment strategy will promptly identify patients for intervention in real-world setting
- Investigations into mechanism of VLN-induced thrombocytopenia are inconclusive
Bleeding Events

CS6-pivotal

- No serious bleeding observed, but increased risk of bleeding events with volanesorsen

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>VLN</th>
<th>Placebo</th>
<th>VLN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients, n (%)</td>
<td>Patients, n (%)</td>
<td>Number of Events</td>
<td>Number of Events</td>
</tr>
<tr>
<td>Hemorrhage SMQ</td>
<td>4 (12%)</td>
<td>16 (49%)</td>
<td>5</td>
<td>45</td>
</tr>
<tr>
<td>Hemorrhage SMQ,</td>
<td>2 (6%)</td>
<td>12 (36%)</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>excluding injection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>site-related events &amp;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lab-related events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td>0</td>
<td>5 (15%)</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Petechiae</td>
<td>0</td>
<td>4 (12%)</td>
<td>0</td>
<td>4</td>
</tr>
</tbody>
</table>

SMQ: Standard MedDRA Query
Platelet Count and Bleeding Events

CS6-pivotal

- Bleeding events occurred at platelet count where spontaneous bleeding not expected
- Concern for VLN effect on platelet function
- Platelet function in patients with FCS not investigated
**Anti-platelet/anticoagulants and Bleeding Events**

CS6-pivotal

- In both placebo and VLN higher proportion of bleeding events on concomitant anti-platelet/anti-coagulant medications
- No significant interaction with anti-platelet/anti-coagulants noted, but small numbers

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th></th>
<th>VLN</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Concomitant anti-plt/anti-coag</td>
<td>Total</td>
<td>Concomitant anti-plt/anti-coag</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2</td>
<td>1</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>27</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>6%</td>
<td>4%</td>
<td>36%</td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>28%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Applicant’s Proposal for Risk Mitigation

#### Dose Adjustments

<table>
<thead>
<tr>
<th>PLT Level</th>
<th>Body Weight &lt;70 kg</th>
<th>Body Weight ≥70 kg</th>
<th>PLT Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (≥140K/uL)</td>
<td>Starting dose: weekly for 3 months Biweekly thereafter</td>
<td>Weekly</td>
<td>Biweekly</td>
</tr>
<tr>
<td>100-140K/uL</td>
<td>Biweekly</td>
<td>Weekly</td>
<td>Biweekly</td>
</tr>
<tr>
<td>75-100K/uL</td>
<td>Biweekly</td>
<td>Biweekly</td>
<td>Weekly</td>
</tr>
<tr>
<td>50-75K/uL</td>
<td>Pause, resume Biweekly when ≥100K/uL</td>
<td>Twice per week until stable</td>
<td></td>
</tr>
<tr>
<td>&lt;50K/uL</td>
<td>Pause, resume biweekly when ≥100K/uL</td>
<td>Daily until stable</td>
<td></td>
</tr>
<tr>
<td>&lt;25K/uL</td>
<td>Discontinue Volanesorsen</td>
<td>Daily until stable</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Pharmacology Review

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

May 10, 2018

Yunzhao Ren, M.D., Ph.D.
DCPII/OCP/OTS/CDER/FDA
Overview of Clinical Pharmacology

- Pharmacokinetics (PK) characteristics of volanesorsen
- Dose selection rationale for Phase 3 Studies
- Assessment of the proposed dosing regimen adjustment
Volanesorsen PK Characteristics

Single Dose Plasma Concentration-Time Profile in Human (Study CS13)

Tissue Exposure in Animals

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Concentration (μg/g) in Cynomolgus Monkey(^1)</th>
<th>AUC(_{0\text{--}\infty}) (μg eq•h/g) in Rat(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>4.03 (C(_{\text{max}}))</td>
<td>51.2</td>
</tr>
<tr>
<td>Liver</td>
<td>278</td>
<td>7310</td>
</tr>
<tr>
<td>Kidney</td>
<td>599</td>
<td>105000</td>
</tr>
<tr>
<td>Bone Marrow</td>
<td>N/A</td>
<td>11700</td>
</tr>
</tbody>
</table>

\(^1\) following 39 week 3 mg/kg volanesorsen once weekly treatment

\(^2\) following single subcutaneous dose of [\(^3\)H]-volanesorsen (5 mg/kg)
Overview of Clinical Pharmacology

• Pharmacokinetics (PK) characteristics of volanesorsen

• Dose selection rationale for Phase 3 Studies
  – Dose- and time-dependent reduction of mean serum apolipoprotein C3 (apoCIII) and triglyceride (TG) concentration
  – Dose- and time-dependent reduction of mean platelet count

• Assessment of the proposed dosing regimen adjustment
Dose Ranging Study CS2

• Study design: randomized, double-blind, placebo-controlled, parallel-group, dose ranging study in adults with severe or uncontrolled hypertriglyceridemia

• Inclusion criteria for fasting TG serum concentration at screening:
  – not on TG-lowering therapy: TG ≥ 440 mg/dL
  – on a stable well-controlled dose of fibrate: TG ≥ 225mg/dL
  – patients with FCS diagnosis

• Treatment (once weekly for 13 weeks):
  – Group 1 and 2: monotherapy of placebo, or volanesorsen 100, 200, or 300 mg (N=57 dosed)
  – Group 3: fibrate + placebo, or volanesorsen 200 or 300 mg (N=28 dosed)
  – Group 4: proof-of-concept, open-label, in patients with FCS (300 mg) (N=3 dosed)
Pharmacodynamic Results: Study CS2

Mean fasting serum apoCIII % change from baseline (monotherapy, N=57)

Results are pooled from group 1 and 2 monotherapy cohorts.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>8.7%</td>
</tr>
<tr>
<td>100 mg Volanesorsen</td>
<td>-40.9%</td>
</tr>
<tr>
<td>200 mg Volanesorsen</td>
<td>-63.2%</td>
</tr>
<tr>
<td>300 mg Volanesorsen</td>
<td>-79.0%</td>
</tr>
</tbody>
</table>

Mean at Week 13
Efficacy Results: Study CS2

Mean fasting serum TG % change from baseline
(monotherapy, N=57)

Results are pooled from group 1 and 2 monotherapy cohorts.

Mean at Week 13

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>25.3%</td>
</tr>
<tr>
<td>100 mg Volanesorsen</td>
<td>-33.9%</td>
</tr>
<tr>
<td>200 mg Volanesorsen</td>
<td>-55.5%</td>
</tr>
<tr>
<td>300 mg Volanesorsen</td>
<td>-68.4%</td>
</tr>
</tbody>
</table>
Platelet Results: Study CS2

Mean platelet counts % change from baseline (N=88)

- Results are from all 4 treatment groups (safety set).
- One patient with FCS experienced severe thrombocytopenia (<50,000/μL) on Day 92, one day after the last dose.

Mean at Week 14

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>4.5%</td>
</tr>
<tr>
<td>100 mg Volanesorsen</td>
<td>-14.2%</td>
</tr>
<tr>
<td>200 mg Volanesorsen</td>
<td>-16.2%</td>
</tr>
<tr>
<td>300 mg Volanesorsen</td>
<td>-23.9%</td>
</tr>
</tbody>
</table>
Overview of Clinical Pharmacology

• Pharmacokinetics (PK) characteristics of volanesorsen

• Dose selection rationale for Phase 3 Studies

• Assessment of the proposed dosing regimen adjustment
  – For mitigation of increased risk of severe thrombocytopenia
    • Two types of platelet reduction
    • Relationship of body weight, drug exposure, and nadir platelet counts
    • Biweekly dosing regimen
Platelet Results: Study CS6

Mean platelet counts % change from baseline in study completers
Another Type of Platelet Reduction

Patient H

Patient D

Patient A

Patient B

Patient G

Patient F

Patient C

Patient E

Platelet Count ($\times 10^3/\mu$L)

Time (Day)

Platelet Count ($\times 10^3/\mu$L)

Time (Day)

Platelet Count ($\times 10^3/\mu$L)

Time (Day)

Platelet Count ($\times 10^3/\mu$L)

Time (Day)

Platelet Count ($\times 10^3/\mu$L)

Time (Day)

Platelet Count ($\times 10^3/\mu$L)

Time (Day)

Platelet Count ($\times 10^3/\mu$L)

Time (Day)

- Treatment Complete
- Switch to biweekly regimen
- Treatment pause/discontinuation

Safety of antisense oligonucleotide and siRNA-based therapeutics.
Chi X et.al, Drug Discov Today. 2017 May;22(5):823-833
Patients Experienced Severe Thrombocytopenia

<table>
<thead>
<tr>
<th>Patient</th>
<th>Study</th>
<th>FCS</th>
<th>Gender</th>
<th>Age (year)</th>
<th>Body Weight (kg)</th>
<th>Clearance (L/h)(^2)</th>
<th>Baseline Platelet Count ((\times 10^3/\mu L))</th>
<th>Nadir Platelet Count ((\times 10^3/\mu L))</th>
<th>Time to Onset</th>
<th>Regimen at Thrombocytopenia(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>CS2</td>
<td>Y</td>
<td>Male</td>
<td>57</td>
<td>68</td>
<td>2.19</td>
<td>101</td>
<td>49</td>
<td>92</td>
<td>Once weekly</td>
</tr>
<tr>
<td>D</td>
<td>CS6</td>
<td>Y</td>
<td>Female</td>
<td>56</td>
<td>52</td>
<td>1.43</td>
<td>184</td>
<td>40</td>
<td>85</td>
<td>Once weekly</td>
</tr>
<tr>
<td>A</td>
<td>CS6</td>
<td>Y</td>
<td>Male</td>
<td>43</td>
<td>111</td>
<td>1.92</td>
<td>210</td>
<td>8</td>
<td>257</td>
<td>Once weekly</td>
</tr>
<tr>
<td>B</td>
<td>CS6</td>
<td>Y</td>
<td>Female</td>
<td>48</td>
<td>56</td>
<td>1.83</td>
<td>247</td>
<td>15</td>
<td>134</td>
<td>Once weekly</td>
</tr>
<tr>
<td>G</td>
<td>CS16</td>
<td>N</td>
<td>Male</td>
<td>55</td>
<td>89</td>
<td>1.54</td>
<td>176</td>
<td>41</td>
<td>51</td>
<td>Once weekly</td>
</tr>
<tr>
<td>F(^4)</td>
<td>CS7</td>
<td>Y</td>
<td>Female</td>
<td>68</td>
<td>42</td>
<td>N/A</td>
<td>277</td>
<td>28</td>
<td>155</td>
<td>Biweekly</td>
</tr>
<tr>
<td>C</td>
<td>CS7</td>
<td>Y</td>
<td>Female</td>
<td>31</td>
<td>62</td>
<td>N/A</td>
<td>238</td>
<td>22</td>
<td>80</td>
<td>Once weekly</td>
</tr>
<tr>
<td>E(^5)</td>
<td>CS7</td>
<td>Y</td>
<td>Female</td>
<td>45</td>
<td>N/A</td>
<td>N/A</td>
<td>213</td>
<td>42</td>
<td>78</td>
<td>Biweekly</td>
</tr>
</tbody>
</table>

\(^1\) as < 50,000/\(\mu L\)

\(^2\) The median volanesorsen clearance is 1.74 L/h from population PK analysis

\(^3\) All patients started with 300 mg once weekly treatment

\(^4\) The subject switched to 300 mg biweekly treatment after first time platelet count <100,000/\(\mu L\) on Day 70 and discontinued study when platelet count <50,000 on Day 155.

\(^5\) The subject switched to 300 mg biweekly treatment after first time platelet count reached 101,000/\(\mu L\) on Day 57 and discontinued study on Day 71 when platelet count reached 80,000/\(\mu L\). The first biweekly dose on Day 71 was not given (patients did not receive any doses for 3 weeks before Day 78).
Overview of Clinical Pharmacology

• Pharmacokinetics (PK) characteristics of volanesorsen

• Dose selection rationale for Phase 3 Studies

• **Assessment of the proposed dosing regimen adjustment**
  – For mitigation of increased risk of severe thrombocytopenia
    • Two types of platelet reduction
    • Relationship of body weight, drug exposure, and nadir platelet counts
    • Biweekly dosing regimen
Body Weight-Nadir Platelet Counts (%Change from Baseline)

Patients from CS6 and CS16 with volanesorsen treatment (N=107)
The Proposed Dosing Regimen

Volanesorsen is contraindicated in patients with low platelet count ($< 140 \times 10^3/\mu L$) before treatment.

<table>
<thead>
<tr>
<th>Platelet Level*</th>
<th>Body Weight $&lt; 70$ kg</th>
<th>Body Weight $\geq 70$ kg</th>
<th>PLT Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ($&gt;140$)</td>
<td>Starting dose: weekly for 3 months Biweekly thereafter</td>
<td>Weekly</td>
<td>Biweekly</td>
</tr>
<tr>
<td>100-140</td>
<td>Biweekly</td>
<td>Weekly</td>
<td>Biweekly</td>
</tr>
<tr>
<td>75-100</td>
<td>Biweekly</td>
<td>Biweekly</td>
<td>Weekly</td>
</tr>
<tr>
<td>50-75</td>
<td>Pause, resume biweekly when $&gt;100$</td>
<td>Twice per week until stable</td>
<td></td>
</tr>
<tr>
<td>$&lt;50$</td>
<td>Pause, resume biweekly when $&gt;100$</td>
<td>Daily until stable</td>
<td></td>
</tr>
<tr>
<td>$&lt;25$</td>
<td>Discontinue Waylivra</td>
<td>Daily until stable</td>
<td></td>
</tr>
</tbody>
</table>

* $\times 10^3/\mu L$
Body Weight-Volanesorsen Clearance

Clearance estimated from Population PK analysis (6 studies, N=256)
Population median CL: 1.78 L/hr

Drug Exposure ↑ with CL ↓

r = 0.42
Nadir Platelet Counts (%Change from Baseline) - Volanesorsen Clearance

Patients from CS6 and CS16 with volanesorsen treatment (N=107)
Assessment of Body Weight-Nadir Platelet Relationship

• Generally there are relationships between body weight, drug exposure, and nadir platelet counts in patients with severe hypertriglyceridemia

  – The relationships capture some extreme cases of Type 1 platelet reduction, which may be used to mitigate platelet reduction in these cases based on body weight/dose.

  – The relationships could not reliably capture Type 2 severe thrombocytopenia cases which comprised ~90% of the observed severe thrombocytopenia.
Assessment of Biweekly Dosing Regimen Switch

- The effect of dosing regimen switch on platelet count in patients < 70 kg and with normal platelet count

- Biweekly dosing regimen switch for mitigation of Type 2 severe thrombocytopenia

- Re-challenge of volanesorsen biweekly treatment after platelet recovery
Subjects Switched from Once Weekly to Biweekly post-Week 13 with Body Weight <70kg

- CS16__Patient J (Body Weight=64 kg)
- CS16__Patient K (Body Weight=45 kg)
- CS16__Patient L (Body Weight=60 kg)

Platelet Count ($\times 10^3/\mu L$):
- 300 mg once weekly regimen period
- 300 mg biweekly regimen period
Platelet Time Profiles of 8 Patients

Patient H

Patient D

Patient A

Patient B

Patient G

Patient F

Patient C

Patient E

Platelet Count ($\times 10^3/\mu L$)

Time (Day)

- Green triangle: Treatment Complete
- Green line: Switch to biweekly regimen
- Red line: Treatment pause/discontinuation
Platelet Time Profiles of 8 Patients

Patient H

Patient D

Patient A

Patient B

Patient G

Patient F

Patient C

Patient E

Platelet Count ($\times 10^3/\mu L$)

Time (Day)

Treatment Complete

Switch to biweekly regimen

Treatment pause/discontinuation
Assessment of Biweekly Dosing Regimen Switch

• The effect of dosing regimen switch on platelet count in patients < 70 kg and with normal platelet count.
  – Inconclusive (only 3 subjects observed)

• Biweekly dosing regimen switch for mitigation of Type 2 severe thrombocytopenia.
  – Does not appear to mitigate the risk.

• Rechallenge of volanesorsen biweekly treatment after platelet recovery
  – Inconclusive due to lack of data
Conclusion of Regimen Adjustment for Mitigation of Increased Risk of Severe Thrombocytopenia

• Relationships between body weight, drug exposure, and nadir platelet counts
  – In Type 1 platelet reduction
    • It is helpful in prediction of extreme cases of Type 1 thrombocytopenia.
    • It may be useful in mitigation of extreme cases of Type 1 thrombocytopenia
      – Body weight cutoff needs to be optimized
      – Dose reduction or dosing frequency reduction
  – In Type 2 platelet reduction
    • It is not reliable for prediction of Type 2 severe thrombocytopenia.
    • Reduction of drug exposure may not be helpful in mitigation of Type 2 severe thrombocytopenia.

• Biweekly regimen switch and re-challenge
  – In Type 1 platelet reduction: inconclusive
  – In Type 2 platelet reduction: Switch did not mitigate; re-challenge is inconclusive
Risk Evaluation and Mitigation Strategy (REMS) Considerations

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

May 10, 2018

Ingrid N. Chapman, PharmD, BCPS
Division of Risk Management (DRISK)
Risk Evaluation and Mitigation Strategy (REMS)

• A risk management plan that utilizes strategies beyond labeling to ensure that the benefits of a drug outweigh the risks

• Designed to achieve specific goals to mitigate risks associated with the use of a drug

• The FDA has authority to require a REMS pre-approval or post-approval
Elements of REMS

• A REMS may include:
  – Medication Guide or patient package insert
  – Communication plan
  – Elements to Assure Safe Use (ETASU)
  – Implementation System

• A REMS must include:
  – Timetable for submission of assessments for New Drug Application (NDA) or Biological License Application (BLA) products
## ETASU REMS Elements

<table>
<thead>
<tr>
<th>Description</th>
<th>ETASU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health care providers who prescribe have particular training or are specially certified</td>
<td>ETASU A</td>
</tr>
<tr>
<td>Pharmacies, practitioners, or health care settings that dispense the drug are specially certified</td>
<td>ETASU B</td>
</tr>
<tr>
<td>The drug be dispensed to patients only in certain health care settings, such as hospitals.</td>
<td>ETASU C</td>
</tr>
<tr>
<td>Documentation of safe-use conditions prior to dispensing such as laboratory testing</td>
<td>ETASU D</td>
</tr>
<tr>
<td>Each patient using the drug be subject to certain monitoring</td>
<td>ETASU E</td>
</tr>
<tr>
<td>Each patient using the drug be enrolled in a registry</td>
<td>ETASU F</td>
</tr>
</tbody>
</table>
Considerations for ETASU

• A product can be approved only if an ETASU is put in place to mitigate the risk

• Cannot be excessively burdensome on patient access to drug, considering in particular, patients with serious or life-threatening diseases or conditions and patients who have difficulty accessing health care

• Must be similar to other products with ETASU that have similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs
Volanesorsen Safety Concerns:

**Risk:** Potential serious bleeding due to severe thrombocytopenia

- Unknown mechanism of volanesorsen-induced thrombocytopenia
- Unpredictable timing and severity of volanesorsen-induced platelet reduction
- Unknown impact of volanesorsen and familial chylomicronemia syndrome on platelet function
What to Accomplish with Risk Mitigation

• Communicate specific safety information to prescribers
  – Potential risk of serious bleeding due to severe thrombocytopenia
  – Reinforce the need to counsel and monitor patients

• Support the patient’s desire to make informed decisions

• Ongoing evaluation of the REMS to support safe use
FDA Proposed REMS Goal

To mitigate the potential risk of serious bleeding due to severe thrombocytopenia associated with volanesorsen by:

1. Ensuring prescribers are educated on the potential risk of serious bleeding due to severe thrombocytopenia

2. Ensuring prescribers are educated and adhere to the following:
   a. Counsel patients on how to recognize and respond to signs and symptoms of serious bleeding
   b. Enroll patients in the REMS Program
   c. Patient monitoring and treatment modifications as described in the Prescribing Information

3. Enrollment of all patients in a registry to further support long-term safety and safe use of volanesorsen
Overview – FDA Proposed REMS

To accomplish the proposed goals, we recommend the following:

• Prescriber certification (ETASU A)
• Pharmacy certification (ETASU B)
• Documentation of safe use conditions (ETASU D)
• Patient monitoring (ETASU E)
• Patient Registry (ETASU F)
• an implementation system and timetable for submission of assessments
FDA Proposed REMS – Prescriber Requirements

• Complete prescriber training and certification

• Enroll in the REMS program using the prescriber enrollment form (one-time enrollment)

• Counsel/enroll patients using the patient-prescriber agreement form

• Complete and submit a patient status form every 90 days to the REMS program
  – Patient status form – the documentation of patient monitoring
  – Collect information about serious bleeding events and platelet declines
FDA Proposed REMS – Pharmacy Requirements

• Designate an authorized representative to enroll in the REMS program using the pharmacy enrollment form

• Prior to dispensing volanesorsen:
  – Verify the prescriber is enrolled in the REMS program
  – Verify the patient is enrolled in the REMS program
FDA Proposed REMS – Patient Requirements

• Receive counseling from the prescriber using the PPAF
  – Risk of serious bleeding due to severe thrombocytopenia
  – Need to monitor platelets during treatment
  – Signs and symptoms of bleeding
  – When to seek medical attention

• Enroll in the REMS program and REMS registry by completing the patient-prescriber agreement form with the prescriber
Risk Mitigation Strategies

FDA and Applicant Proposed REMS Alignment

• Prescriber Certification ✓
• Pharmacy Certification ✓
• Documentation of safe use conditions ✓
• Patient Monitoring ✓
• REMS Registry ✓
Patient Support Program

**Purpose**: to ensure patient safety by maximizing compliance with platelet monitoring and dose adjustments as recommended in the prescribing information

- These activities are outside of the REMS
- No authority to enforce voluntary activities
FDA Proposed REMS

REMS Capabilities
• Prescribers are educated about the risk and the need to carefully monitor for thrombocytopenia and bleeding
• Patients are aware of the risk and the need for frequent monitoring
• Patient registry further supports long-term safety and safe use of volanesorsen

REMS Limitations
• Rapid and severe decreases in platelets may not be prevented even with:
  – Compliance with enhanced platelet monitoring
  – Dose modifications per the prescribing information
• Will not enforce monitoring as described in the prescribing information
Benefit/Risk Summary

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

May 10, 2018

Mary Dunne Roberts, MD
Summary of Condition

• FCS is a rare, autosomal recessive, genetic condition
  – 1 to 2 per 1 million individuals
• Pancreatitis is the most serious consequence
• Patients experience other symptoms which may be severe
• FCS and other forms of severe hypertriglyceridermia may overlap in clinical presentation
• Accurate diagnosis of FCS may be challenging
• Diet is effective but difficult
• Safe and effective therapies are needed
Benefit/Risk Profile of VLN

Benefits
• Compelling reduction in TG in patients with FCS who are refractory to treatment with other TG-lowering medications
• Magnitude of direct benefit to patients with FCS uncertain

Risks
• VLN causes thrombocytopenia of unknown etiology, with the potential for serious bleeding. Unable to predict:
  – Which patients will be affected
  – Timing of precipitous platelet reductions
• Serious hypersensitivity, with the potential contribution of anti-VLN antibodies
• Injection site reactions and possibility of persistent discoloration
• Imbalances in flu-like reactions, renal and hepatic biomarkers

Benefit/risk of VLN and feasibility of platelet monitoring in children has not been studied
Proposed Approach to Reduce Risk of Serious Bleeding with Thrombocytopenia

- Proposed Dosing strategy
  - Not prospectively tested
  - Current data is inconclusive to support biweekly dosing based on body weight

- Proposed Platelet testing
  - Applicant has proposed every two week monitoring at a minimum for a chronic therapy
  - In a clinical trial, platelet testing every 1 to 2 weeks did not prevent patients from experiencing a platelet count < 25 K/μL

- In real world setting the feasibility of frequent monitoring for life-long therapy unknown

- Uncertainties may impact the ability of the REMS to ensure that the benefit outweighs risk