FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE (EMDAC) MEETING

Thursday, May 10, 2018
7:59 a.m. to 5:34 p.m.

Tommy Douglas Conference Center
10000 New Hampshire Avenue
Silver Spring, Maryland
Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

LaToya Bonner, PharmD, NCPS
Division of Advisory Committee and
Consultant Management
Office of Executive Programs, CDER, FDA

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY
COMMITTEE MEMBERS (Voting)

Daniel Budnitz, MD, MPH
CAPT, US Public Health Service
Director, Medication Safety Program
Division of Healthcare Quality Promotion
Centers for Disease Control and Prevention
Atlanta, Georgia

Kenneth D. Burman, MD
Chief, Endocrine Section
Medstar Washington Hospital Center
Professor, Department of Medicine
Georgetown University
Washington, District of Columbia
Brendan M. Everett, MD, MPH
Assistant Professor of Medicine
Harvard Medical School
Director, General Cardiology Inpatient Service
Brigham and Women’s Hospital
Boston, Massachusetts

Cecilia C. Low Wang, MD, FACP
Associate Professor of Medicine
Director, Glucose Management Team
University of Colorado Hospital
Associate Director, Fellowship/Education
Division of Endocrinology, Metabolism and Diabetes
University of Colorado Anschutz Medical Campus/School of Medicine
Medical Safety Officer and Safety Lead
CPC Clinical Research
Aurora, Colorado
James D. Neaton, PhD
Professor of Biostatistics
Division of Biostatistics
Coordinating Centers for Biometric Research
School of Public Health
University of Minnesota
Minneapolis, Minnesota

Thomas J. Weber, MD
Associate Professor, Endocrinology,
Metabolism and Nutrition
Duke University Medical Center
Durham, North Carolina

Peter W. F. Wilson, MD
(Chairperson)
Director, Epidemiology and Genomic Medicine
Atlanta Veterans Administration Medical Center
Professor of Medicine and Public Health
Emory University
Emory Clinical Cardiovascular Research Institute
Atlanta, Georgia
Susan Z. Yanovski, MD
Co-Director, Office of Obesity Research
Senior Scientific Advisor for Clinical Obesity Research
National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (NIH)
Bethesda, Maryland

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE MEMBERS (Non-Voting)
Reshma Kewalramani, MD
(Industry Representative)
EVP, Global Medicines Development and Medical Affairs
Chief Medical Officer
Vertex Pharmaceuticals Incorporated
Boston, Massachusetts
TEMPORARY MEMBERS (Voting)

Nichole Cuaresma
(Patient Representative)
Anchorage, Alaska

Michael S. Epstein, MD, FACG, AGAF
Founder and Principle Physician
Digestive Disorders Associates
President, Maryland Diagnostic & Therapeutic Endo Center
Annapolis, Maryland

Robert Kane, MD, PA
Advisor and Consultant
Adjunct Professor
University of South Carolina College of Pharmacy
Nokomis, Florida

Anna McCollister-Slipp
(Acting Consumer Representative)
Founder, VitalCrowd
Washington, District of Columbia
Elaine H. Morrato, DrPH, MPH
Associate Dean for Public Health Practice
Associate Professor
Department of Health Systems, Management and Policy
Colorado School of Public Health
University of Colorado Anschutz Medical Campus
Aurora, Colorado

Connie B. Newman, MD, FACP, FAHA, FAMWA
Adjunct Professor of Medicine
New York University School of Medicine
Attending Physician
Department of Veterans Affairs
New York Harbor Healthcare Center
New York, New York

Thomas L. Ortel, MD, PhD
Chief, Division of Hematology
Professor of Medicine & Pathology
Medical Director, Clinical Coagulation Laboratory
Duke University Medical Center
Durham, North Carolina
Jean-Pierre Raufman, MD
Moses and Helen Golden Paulson Professor of Medicine
Head, Division of Gastroenterology & Hepatology
University of Maryland School of Medicine
Baltimore, Maryland

Meghan Rowcliffe, PharmD, BCPS, BCPPS
Pediatric Medication Safety Officer
The Johns Hopkins Hospital
Baltimore, Maryland

Robert Shamburek, MD
Senior Staff Clinician
Cardiovascular and Pulmonary Branch
National Heart, Lung, and Blood Institute, NIH
Bethesda, Maryland
Susan M. Sinclair, PhD, MPH, RN
Professor, School of Nursing
College of Health and Human Services
University of North Carolina Wilmington
Wilmington, North Carolina

David F. Stroncek, MD
Director, Center for Cellular Engineering
Department of Transfusion Medicine
NIH Clinical Center
Bethesda, Maryland

FDA PARTICIPANTS (Non-Voting)
Mary T. Thanh Hai, MD
Acting Director
Office of Drug Evaluation II (ODE-II)
Office of New Drugs (OND), CDER, FDA
James P. Smith, MD, MS
Deputy Director
Division of Metabolism and Endocrinology Products (DMEP)
ODE-II, OND, CDER, FDA

John Sharretts, MD
Clinical Team Lead (acting)
DMEP, ODE-II, OND, CDER, FDA

Mary D. Roberts, MD
Clinical Reviewer
DMEP, ODE-II, OND, CDER, FDA

Cynthia LaCivita, PharmD
Director, Division of Risk Management (DRISK)
Office of Medication Error and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
CDER, FDA
### CONTENTS

<table>
<thead>
<tr>
<th>AGENDA ITEM</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Call to Order and Introduction of Committee</td>
<td></td>
</tr>
<tr>
<td>Peter Wilson, MD</td>
<td>14</td>
</tr>
<tr>
<td>Conflict of Interest Statement</td>
<td></td>
</tr>
<tr>
<td>LaToya Bonner, PharmD</td>
<td>19</td>
</tr>
<tr>
<td>FDA Introductory Remarks</td>
<td></td>
</tr>
<tr>
<td>John Sharretts, MD</td>
<td>23</td>
</tr>
<tr>
<td><strong>Applicant Presentations – Akcea Therapeutics</strong></td>
<td></td>
</tr>
<tr>
<td>Introduction</td>
<td></td>
</tr>
<tr>
<td>Louis St.L. O'Dea, MB, BCh, BAO, CSPQ, FRCP(C)</td>
<td>33</td>
</tr>
<tr>
<td>Unmet Need: Disease Background</td>
<td></td>
</tr>
<tr>
<td>Daniel Rader, MD</td>
<td>42</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td>Steve Freedman, MD, PhD</td>
<td>49</td>
</tr>
<tr>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Louis St.L. O'Dea, MB, BCh, BAO, CSPQ, FRCP(C)</td>
<td>55</td>
</tr>
</tbody>
</table>

*Note: The page numbers provided are placeholders.**
**CONTENTS (continued)**

<table>
<thead>
<tr>
<th>AGENDA ITEM</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>Walter Singleton, MD</td>
<td>74</td>
</tr>
<tr>
<td>Risk Management</td>
<td></td>
</tr>
<tr>
<td>Michael Stevenson, RPh, PhD</td>
<td>82</td>
</tr>
<tr>
<td>Clinical Perspective</td>
<td></td>
</tr>
<tr>
<td>Seth Baum, MD, FACC, FACPM, FAHA, FNLA, FASPC</td>
<td>89</td>
</tr>
<tr>
<td>Clarifying Questions to Applicant</td>
<td>93</td>
</tr>
<tr>
<td><strong>FDA Presentations</strong></td>
<td></td>
</tr>
<tr>
<td>Clinical Review Introduction</td>
<td></td>
</tr>
<tr>
<td>Mary Roberts, MD</td>
<td>127</td>
</tr>
<tr>
<td>Statistical Review of Efficacy</td>
<td></td>
</tr>
<tr>
<td>Alexander Cambon, PhD</td>
<td>137</td>
</tr>
<tr>
<td>Clinical Review</td>
<td></td>
</tr>
<tr>
<td>Mary Roberts, MD</td>
<td>156</td>
</tr>
<tr>
<td>Clinical Pharmacology Review</td>
<td></td>
</tr>
<tr>
<td>Yunzhao Ren, MD, PhD</td>
<td>180</td>
</tr>
<tr>
<td>Risk Evaluation and Mitigation Strategy</td>
<td></td>
</tr>
<tr>
<td>(REMS) Considerations</td>
<td></td>
</tr>
<tr>
<td>Ingrid Chapman, PharmD, BCPS</td>
<td>197</td>
</tr>
<tr>
<td>AGENDA ITEM</td>
<td>PAGE</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>------</td>
</tr>
<tr>
<td>Benefit/Risk Summary</td>
<td>204</td>
</tr>
<tr>
<td>Mary Roberts, MD</td>
<td>209</td>
</tr>
<tr>
<td>Clarifying Questions to FDA</td>
<td>214</td>
</tr>
<tr>
<td>Open Public Hearing</td>
<td>265</td>
</tr>
<tr>
<td>Clarifying Questions (continued)</td>
<td>319</td>
</tr>
<tr>
<td>Questions to the Committee and Discussion</td>
<td>439</td>
</tr>
<tr>
<td>Adjournment</td>
<td></td>
</tr>
</tbody>
</table>
PROCEEDINGS

(7:59 a.m.)

Call to Order

Introduction of Committee

DR. WILSON: Good morning. Welcome to the EMDAC meeting. First, I would like to remind everyone to please silence your phones, pull out your phones, remember to silence it and any other devices if you've not already done so.

We have a variety of things to do as we start out here. First is identify the FDA press contact, Lauren Smith Dyer. Is Lauren here? She's in the back corner there.

So I'm Peter Wilson. I'm the chair of the Endocrinologic and Metabolic Drugs Advisory Committee and I'll be chairing the meeting, and we're now calling the meeting to order. We'll start by going around the table and each person will introduce himself or herself. And we'll start to the left here with FDA.

DR. THANH HAI: Good morning. I'm Dr. Thanh Hai. I'm an acting director in the Office of Drug
Evaluation II.

DR. SMITH: Good morning. I'm Jim Smith. I'm deputy division director of Division of Metabolism and Endocrinology Products.

DR. SHARRETTS: Good morning. I'm John Sharretts. I'm acting clinical team leader in the Division of Metabolism and Endocrinology Products.

DR. ROBERTS: Morning. I'm Mary Roberts. I'm the clinical reviewer for the Division of Metabolism and Endocrinology Products.

DR. LaCIVITA: Good morning. My name is Cynthia LaCivita. I'm the director for the Division of Risk Management in the Office of Surveillance and Epidemiology.

DR. SINCLAIR: Good morning. I'm Susan Sinclair from the University of North Carolina Wilmington. I'm an epidemiologist and I'm in the clinical research program.

DR. NEATON: Jim Neaton, University of Minnesota, biostatistician.

DR. EPSTEIN: Michael Epstein, private
practice, gastroenterologist and hepatologist in Annapolis, Maryland, and I run a clinical research program.

DR. LOW WANG: Cecilia Low Wang, University of Colorado in Denver. I'm an endocrinologist.

DR. NEWMAN: Connie Newman. I'm from New York University School of Medicine in New York. I'm an endocrinologist with an interest in lipids and cardiovascular disease.

DR. WEBER: Tom Weber, endocrinologist at Duke University.

DR. STRONCEK: Dave Stroncek, hematologist from the NIH Clinical Center, Bethesda, Maryland.

DR. EVERETT: Brendan Everett. I'm a cardiologist at the Brigham and Women's Hospital in Harvard Medical School in Boston.

DR. BONNER: Good morning. Latoya Bonner, DFO for EMDAC.

DR. WILSON: Peter Wilson, preventive cardiology, endocrinology, and lipidology at Emory University.

DR. BUDNITZ: Dan Budnitz, epidemiologist
and medical officer, medication safety program at CDC.

DR. MORRATO: Good morning, Elaine Morrato, epidemiologist and also a professor in health systems management and policy and associate dean for public health practice at the Colorado School of Public Health.

DR. BURMAN: Good morning. Ken Burman, a professor of medicine at Georgetown University and head of endocrine at MedStar Washington Hospital Center.

MS. CUARESMA: Hi, good morning. I'm Nicole Cuaresma. I'm a patient representative.

DR. SHAMBUREK: I'm Bob Shamburek. I run the intramural NHLBI lipid clinic and I'm a lipidologist and gastroenterologist.

DR. ORTEL: Good morning. Tom Ortel from Duke, and I'm a hematologist specializing in hemostasis and thrombosis.

DR. YANOVSKI: Susan Yanovski. I'm co-director of the Office of Obesity Research at the National Institute of Diabetes, Digestive, and
Kidney Diseases.

DR. RAUFMAN: Jean-Pierre Raufman. I'm chair of the GI Drug Advisory Committee and chief of gastroenterology at the University of Maryland.

DR. KANE: Good morning, Robert Kane. I'm a hematologist.

DR. KEWALRAMANI: Good morning. Reshma Kewalramani. I'm the chief medical officer at Vertex and I'm the industry representative.

DR. WILSON: Thank you very much. So for topics such as those being discussed at today's meeting, there are often many varied opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption.

Thus, as a general reminder, individuals will be allowed to speak into the record only if recognized by the chair and we look forward to a productive meeting using this method. In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the
advisory committee members take care that their
conversations about the topics at hand take place
in the open forum of the meeting.

We are aware that members of the media are
anxious to speak with the FDA about these
proceedings. However, FDA will refrain from
discussing the details of this meeting with the
media until its conclusion. Also, the committee is
reminded to please refrain from discussing the
meeting topics during breaks or lunch. So thank
you. Now, over to Commander Latoya Bonner.

Conflict of Interest Statement

DR. BONNER: Good morning. The Food and
Drug Administration is convening today for the
meeting of the Endocrinologic and Metabolic Drugs
Advisory Committee under the authority of the
Federal Advisory Committee Act of 1972.

With the exception of the industry
representatives, all members and temporary voting
members of the committees are special government
employees or regular federal employees from other
agencies and are subject to federal conflict of
interest laws and regulations.

The following information on the status of the committees’ compliance with the federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208 is being provided to participants in today’s meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with the federal ethics and conflict of interest laws.

Under 18 U.S.C., Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency’s need for a special government employee’s services outweighs his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.
Related to the discussions at today's meetings, members and temporary voting members of the committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses and minor children, and for purposes of 18 U.S.C. Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of the safety and efficacy of new drug application 210645 for volanesorsen solution for subcutaneous injection, submitted by Akcea Therapeutics, Incorporated.

The proposed indication is as an adjunct to diet for the treatment of patients with familial chylomicronemia syndrome.

This is a particular matters meeting during which specific matters related to Akcea Therapeutics's NDA will be discussed. Based on the
agenda for today's meeting and all financial
interests reported by the committee members and
temporary voting members, no conflict of interest
waivers have been issued in connection with this
meeting.

To ensure transparency, we encourage all
standing committee members and temporary voting
members to disclose any public statements that they
have made concerning the product at issue.

With respect to FDA's invited industry
representatives, we would like to disclose that
Dr. Reshma Kewalramani is participating in this
meeting as a non-voting industry representative
acting on behalf of regulated industry.
Dr. Kewalramani's role at this meeting is to
represent industry in general and not any
particular company. Dr. Kewalramani is employed by
Vertex Pharmaceuticals.

We would like to remind members and
temporary voting members that if the discussions
involve any other products or firms not already on
the agenda for which an FDA participant has a
personal or imputed financial interest, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with the firm at issue. Thank you.

DR. WILSON: Thanks very much. So our next step is we're going to proceed with the FDA's introductory remarks from Dr. John Sharretts.

FDA Introductory Remarks - John Sharretts

DR. SHARRETTTS: Good morning. My name is John Sharretts. I am an acting clinical team leader in the Division of Metabolism and Endocrinology Products. Thank you for being here today. We look forward to an informative discussion.

The purpose of today's meeting is to discuss the use of the drug volanesorsen as an adjunct to diet for the treatment of hypertriglyceridemia in patients with familial chylomicronemia syndrome or
FCS.

FCS comprises a group of autosomal recessive disorders, characterized by the inability to process dietary fats due to very low lipoprotein lipase activity. Fat from the diet accumulates in the form of chylomicron in the blood and these chylomicrons contribute to very high triglyceride levels.

Patients with FCS manifest characteristic signs and symptoms such as recurrent acute pancreatitis, abdominal pain, lipemia retinalis, and eruptive cutaneous xanthomas. FCS is very rare. The cited prevalence is 1 to 2 per million and patients with FCS represent only a small fraction of patients with severely elevated triglycerides.

Other conditions such as diabetes or obesity are far more likely to cause very severe hypertriglyceridemia. This distinction is important because patients with more common causes of very high triglycerides may have very different benefit-risk considerations from volanesorsen,
including alternate treatment options than patients with FCS.

As you will learn later this morning, the FDA review team generally agrees with the applicant's major finding, that volanesorsen can lower triglycerides substantially.

Changes in fasting triglycerides have been used for many decades to support approval of drugs intended to treat severe hypertriglyceridemia on the assumption that TG lowering will decrease the risk of acute pancreatitis.

A challenge with relying on a surrogate endpoint, however, is that the magnitude of the clinical benefit remains uncertain. Accordingly, an estimate of volanesorsen treatment effect on clinical outcomes, large or small, would help guide the overall benefit-risk assessment.

To be clear, the purpose of this meeting is not to re-adjudicate the use of triglycerides as a surrogate for clinical endpoints, but instead to discuss the benefits of volanesorsen specifically in the intended population, considering the risks
of this drug.

If volanesorsen had a reassuring safety profile, even a small clinical benefit associated with the observed decrease in TG could lead to a favorable benefit-risk assessment. With this application, however, we are required to balance the effect of volanesorsen on a surrogate endpoint against substantial risk.

As you will learn, the review team has found this assessment to be a considerable challenge. Despite very intensive laboratory monitoring, some patients treated with volanesorsen experienced unpredictable rapid decreases in platelet counts below 50,000 per microliter that, in some cases, required hospitalization and additional treatment.

Drug-induced thrombocytopenia in this range can be associated with serious or fatal bleeding events. We are not reassured by the observation that no serious or fatal bleeding event has occurred to date because the development program was small, as expected for evaluation of a rare disease.
Furthermore, there was an increased risk for bleeding related adverse events such as petechiae and epistaxis with volanesorsen in the pivotal trial. Our discussion therefore will ultimately focus on the overall assessment of clinical benefit and risk.

Today's speakers will consider the effect of volanesorsen on clinically meaningful outcomes such as abdominal pain and other symptoms that might be important to patients with FCS as well as the overall safety of the drug, including adverse events other than thrombocytopenia.

Additionally, we will address the high rates of drug discontinuation due to safety tolerability. Drug discontinuation affects interpretation of the clinical trials and impacts the potential effect size in a real-world setting.

Now, we will turn to today's agenda. After my introduction, the applicant will present to you their view of the efficacy and safety of volanesorsen followed by a series of presentations by the FDA reviewers.
From the FDA, you will hear from Dr. Mary Roberts, the clinical reviewer, Dr. Alex Cambon, the statistical reviewer, Dr. Yunzhao Ren, the clinical pharmacology reviewer, and Dr. Ingrid Chapman, the risk management analyst.

You will have the opportunity to ask clarifying questions following each set of presentations. After that, we'll break for lunch and return for the open public hearing. Then we'll move on to the discussion points, which I would like to introduce now.

The first discussion question addresses volanesorsen's clinical benefit. Now, once again, we are not asking you to readjudicate TG as a surrogate endpoint. Instead, we would like to understand your view of the benefits of this drug for patients with FCS, including how the observed TG-lowering effect informs labeling that includes a proposed dosing strategy not studied in clinical trials and the effect of drug discontinuation on efficacy beyond 3 months.

Because the applicant has proposed labeling
claims regarding volanesorsen's effect on
pancreatitis and abdominal pain, we ask for your
assessment of those endpoints specifically.

Finally, we ask you to consider all the
efficacy data, both TG and clinical endpoints, to
characterize the overall magnitude of clinical
benefit.

Question 2 asks you to discuss the safety
and tolerability of volanesorsen, focusing on
adverse events other than thrombocytopenia and
bleeding, such as injection site reactions, immune-
related events such as serum sickness, and
hypersensitivity events such as anaphylaxis.

Question 3 addresses thrombocytopenia. This
discussion point asks you to describe your overall
concern for the risk of thrombocytopenia and
bleeding and your assessment of the adequacy of the
proposed monitoring strategy, the feasibility of
intensive monitoring on clinical practice and the
evidence to support the proposed dosing algorithm.

The fourth question asks you to consider the
intended population. This discussion point asks if
you believe that the term familial chylomicronemia syndrome, without further definition, sufficiently identifies the patient population for whom volanesorsen may have a favorable benefit-risk profile or whether you have alternative suggestions to define the appropriate population.

Question 5 asks you to discuss whether you think a risk evaluation and mitigation strategy or REMS is necessary, whether it would be able to ensure that the benefits outweigh the risks of bleeding due to thrombocytopenia, and if you recommend any changes if volanesorsen were to be approved with a REMS.

Although you will hear the FDA proposal for a REMS, you should not infer that FDA has already determined that volanesorsen has a favorable benefit-risk assessment to support approval with such a REMS in place. Instead, the discussion today is intended to inform our decision making.

Question 6 addresses the possibility that, if the drug is approved, clinicians might use volanesorsen in pediatric patients, who have not
been studied in the volanesorsen development program. We would like to hear your level of concern with respect to the potential use and your recommendations for future study in this population.

Finally, question 7 is a voting question, which I will read verbatim. Based on the information included in the briefing materials and presented today, has the applicant provided sufficient efficacy and safety data to support approval of volanesorsen?

If yes, provide your rationale and any recommendations regarding the indicated patient population, dosing, clinical monitoring, risk management strategies, and/or post-marketing studies. If no, provide your rationale and comment on what additional data would be required to support approval.

I cannot emphasize enough that the details of your comments and discussion following your vote are as important if not more important in informing our decision making than the vote tally itself.
With that, I will stop and turn the program back over to the AC chair. Thank you again for joining us for this important discussion.

DR. WILSON: Thanks very much. Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, the FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships.
If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking. So now, we'll proceed with Akcea's presentations.

**Applicant Presentation – Louis O'Dea**

DR. O'DEA: Good morning. I'm Louis O'Dea, medical officer and head of regulatory affairs for Akcea Therapeutics. We appreciate the opportunity to present our data and I'd like to thank the members of the committee for their commitment to this process and for reviewing the pre-meeting materials.

Today, we will discuss volanesorsen, a novel antisense therapy that represents the first effective treatment for patients with familial chylomicronemia syndrome or FCS, a rare metabolic disease with a high unmet medical need.

The cardinal feature of FCS is very high plasma triglyceride levels, unresponsive to available lipid-lowering therapies. While there are many symptoms associated with the disease, the
major cause of morbidity and mortality is acute pancreatitis, which can lead to multi-organ failure, chronic pancreatitis, and even death.

Volanesorsen demonstrated significant triglyceride reduction with decreases of more than 90 percent from baseline relative to placebo, levels low enough to reduce the risk of pancreatitis.

We've characterized the safety profile, in particular related to the identified risk of treatment-related thrombocytopenia. Importantly, we developed a comprehensive risk management program which will support patient safety and continue to collect efficacy and safety data on a long-term basis.

FCS has significant clinical consequences. It is characterized by the presence of chylomicrons, which are circulating in triglyceride-rich particles, shown here as the milky plasma in a blood sample.

Chylomicrons arise from normal digestion and are typically metabolized through downstream lipids.
to fatty acids. However, for patients lacking the important enzyme to metabolized chylomicrons, lipoprotein lipase, FCS is characterized by persistent high levels of triglycerides, 10 to 30 times the upper limit of normal.

As you will hear from Dr. Rader, this metabolic disorder causes a multitude of symptoms, including recurrent abdominal pain, xanthomata, and can have the serious and life-threatening consequence of pancreatitis. Despite the severity of FCS, there are currently no approved pharmacologic agents to treat patients.

Existing drugs for hypertriglyceridemia are not effective as they require functioning lipoprotein lipase or LPL. Restrictive fat diet, the first and essentially only current course of treatment, also fails to adequately lower triglycerides, as you will see in the baseline triglyceride values of our study population.

Therefore, patients remain at risk for pancreatitis and the other burdens of their disease.
So let me describe what causes FCS and how volanesorsen works in regards to the pathogenesis of this disease. To understand the specific defect that causes FCS, we must briefly consider the origin and processing of triglycerides and chylomicrons. Triglycerides arise from two sources, internally from the formation of VLDL by the liver and externally from food in the form of chylomicrons.

Under normal circumstances, chylomicrons are transient and metabolize by lipoprotein lipase and the resulting triglycerides are processed to fatty acids for use as fuel or to be stored for later use.

apoC-III modulates the process by negatively regulating lipoprotein lipase activity. Normal plasma, when drawn, is clear. In patients with FCS, lipoprotein lipase is defective. The functional deficiency can arise from genetic abnormalities in lipoprotein lipase itself or its many regulatory elements.

In all cases, the final common pathway is
impaired lipoprotein lipase function, leading to chylomicron accumulation. And this creates the milky-appearing plasma, where we can measure chylomicrons using standard tests for triglycerides.

Our initial studies with volanesorsen revealed an additional apoC-III-dependent lipoprotein lipase-independent metabolic pathway that's also involved in chylomicron clearance. Inhibiting this pathway with volanesorsen, which blocks apoC-III, facilitates chylomicron and triglyceride metabolism.

Removing the break on chylomicron clearance reduces their accumulation in patients with FCS. Our approach is to use antisense technology to block apoC-III production. Under normal circumstances, apoC-III gene is transcribed to messenger RNA and this messenger RNA is then translated into apoC-III protein.

Antisense technology uses a complimentary sequence to target the messenger RNA and this messenger RNA is then translated into apoC-III
protein. Antisense technology uses a complimentary sequence to target the messenger RNA of a target protein for degradation, which blocks the process and facilitates the clearance of the accumulated chylomicrons.

The proposed indication for volanesorsen is as an adjunct to diet for the treatment of adult patients with familial chylomicronemia syndrome. We're committed to treating only the small fraction of patients diagnosed with FCS and these are the patients who have the highest unmet medical need.

In regards to dosing, volanesorsen comes as a single use pre-filled syringe of 300 milligrams and is suitable for self-administration subcutaneously. Our clinical trials used a starting dose of 300 milligrams and included a dose-adjustment paradigm. The proposed label includes a similar paradigm, but one that incorporates body weight as an additional conservative basis for dose adjustment.

Volanesorsen's long half-life allows dosing adjustment through dose frequency modification. As
part of our post-approval commitment, we're
proposing a comprehensive risk management program
with five important components that work together
to support patient safety and compliance. Our
labeling provides details regarding patient
selection, treatment, with instructions on dose
adjustments and platelet monitoring.

We're collaborating with the agency to
develop a risk evaluation and mitigation strategy,
with added elements to assure safe use. It will
include mandatory registration of all patients,
prescribers, and pharmacies. Distribution will be
controlled through specialty pharmacies, with
dispensing limited to a month's supply.

Enhanced pharmacovigilance will closely
monitor product use and assess long-term safety,
including identifying potential product risks and
the effectiveness of the risk management program.
We also plan to initiate a 5-year global treatment
registry study to prospectively collect additional
safety and efficacy data post-approval.

Supporting all of this is the patient
support program. Nurse case managers will facilitate patient compliance and access to platelet testing, including mobile testing and compliance when away from home.

Our proposed integrated risk management program will assure that only patients with FCS will be treated with volanesorsen. Our commitment includes multiple pathways to support compliance and to ease the burden of monitoring patients and physicians.

So with this short background in mind, here’s the agenda for the remainder of our presentation. Dr. Dan Rader will discuss the disease background and the diagnosis of FCS and the need for a new therapy based on his experience treating these patients.

Dr. Steven Freedman, an expert on pancreatitis, will then describe triglyceride-associated pancreatitis. I will return to present the efficacy data from the clinical trials of volanesorsen and Dr. Walter Singleton, the former chief medical officer of Ionis, will discuss the
safety data.

Dr. Michael Stevenson, the head of medical affairs at Akcea Therapeutics, will describe our risk management program, including our proposed REMS. Dr. Seth Baum, who treats patients with FCS and has experience treating patients with volanesorsen, will then close the presentation with his clinical perspective.

We also have additional experts with us here today. All experts have been compensated for their time and travel to today's meeting. And so thank you and, with that, I'll turn the presentation over to Dr. Rader.

DR. WILSON: Dr. Rader, before you start, we have a new member of our committee who has joined. Would she please introduce herself? And we put that into the record and where you are from.

MS. McCOLLISTER-SLIPP: Hi, I'm actually not Meghan Rowcliffe. I'm Anna McCollister-Slipp. I just didn't see my name placard. I'm one of the consumer representatives on the advisory committee.

DR. WILSON: Your name?
MS. McCOLLISTER-SLIPP: It's Anna McCollister-Slipp.

DR. WILSON: Thanks very much. We have a chair for you to sit down here. So if you could move down there --

MS. McCOLLISTER-SLIPP: Thank you.

DR. WILSON: Thanks very much. We have yet another one, a member of our committee. So would you please take your chair, introduce yourself and where you're from?

DR. ROWCLIFFE: Thank you. I'm Meghan Rowcliffe. I'm a medication safety officer at Johns Hopkins Hospital.

DR. WILSON: Thanks very much, Dr. Rader. Go ahead.

Applicant Presentation – Daniel Rader

DR. RADER: Good morning. I'm Dan Rader, professor of molecular medicine and chair of the Department of Genetics at the University of Pennsylvania.

I'm engaged in research involving the genetics of lipid metabolism and a practicing
clinician focused on patients with genetic disorders with lipid metabolism. Over the next few minutes, I will review the characteristics of this very rare disease and the impact that FCS has on our patients.

Familial chylomicronemia syndrome or FCS is an ultra rare serious metabolic disorder characterized by extremely elevated chylomicrons due to impaired chylomicron clearance.

Underlying causes of FCS include mutations in the genes encoding lipoprotein lipase or LPL or other LPL regulatory proteins that enable LPL activity and effective chylomicron clearance.

FCS is characterized by severe chylomicronemia, which is assessed by measuring fasting triglycerides, as chylomicrons are not routinely measured in clinical practice. Fasting triglycerides above 750 milligrams per deciliter are generally indicative of chylomicronemia.

One of the key consequences of FCS is pancreatitis, which can be potentially life-threatening and which you will hear more about from
Dr. Freedman.

Now, let's review the clinical presentation of FCS. A key element of the FCS clinical presentation is severe and persistent hypertriglyceridemia which is refractory to currently available lipid-lowering medications such as fibrates and fish oils and a restricted fat diet.

FCS often presents in childhood with severe hypertriglyceridemia or pancreatitis, although patients may be diagnosed at any age. A family history of hypertriglyceridemia may be present, though is not required for this autosomal recessive genetic condition. There is often a history of pancreatitis or unexplained abdominal pain.

Finally, the presence of secondary causes of hypertriglyceridemia such as poorly controlled diabetes, excessive alcohol use, or certain medications makes the diagnosis of FCS less likely and serves to help differentiate from other causes of chylomicronemia.

The diagnosis of FCS has traditionally been
made clinically based on the clinical presentation that I just reviewed. When FCS is suspected, the clinical diagnosis can be supported by low post-heparin plasma LPL activity of less than 20 percent of normal.

However, this assay is not currently available clinically outside the research setting. Genetic testing for the identification of mutations in genes involved in the LPL pathway can help confirm the diagnosis.

These mutations may be homozygous, compound heterozygous, or rarely double heterozygous involving two different genes. However, it is likely that additional genes may cause FCS and therefore negative genetic testing does not exclude the diagnosis of FCS.

Patients with FCS represent a very small subgroup of those with elevated triglyceride levels. To contextualize the rarity of FCS, this figure shows the distribution of hypertriglyceridemia in the general population.

Starting from the bottom of this pyramid,
normal, fasting triglycerides are considered to be
less than 150 milligram per deciliter and
constitute the majority of the general population.

Approximately 28 percent of the population
have fasting triglycerides greater than 150
milligram per deciliter, which are generally
considered to be elevated. Those with
chylomicronemia, that is, a measured triglyceride
level in excess of 750 milligram per deciliter,
represent only approximately 0.1 percent of the
general population.

Importantly, the majority of these patients
have obesity, uncontrolled diabetes, excessive
alcohol use, or other medications known to elevate
triglyceride levels. These patients also generally
have at least some response to triglyceride-
lowering therapy.

Importantly, patients with FCS represent
only a minor fraction of patients with
chylomicronemia. In contrast to the broader group,
patients with FCS have persistent triglycerides
greater than 750, are absent of secondary causes,
and are not responsive to triglyceride-lowering therapies, indicating that they have low LPL activity.

While the true prevalence of FCS has not been systematically evaluated, the best estimates suggest that it is approximately 1 to 4 patients with FCS per 1 million individuals. This is the well-defined ultra rare group of patients with the highest unmet medical need that we're focusing on today.

Because the complications of FCS are due to chylomicronemia, triglyceride reduction is the main goal of therapy in patients with FCS. The major treatment goal in FCS includes reduction of pancreatitis risk.

Another goal of treatment is the reduction in the other symptoms and associated disease burden in this condition. Chylomicron lowering is assessed through reduction in fasting triglyceride levels.

As Dr. Freedman will present, pancreatitis risk correlates with triglyceride levels; the
higher the triglyceride, the higher the risk of pancreatitis. A substantial reduction in triglycerides is expected to decrease the risk of pancreatitis.

Unfortunately, there are no effective therapeutic interventions for patients with FCS. Patients with FCS are generally refractory to triglyceride-lowering medications such as fibrates and fish oils. This is due to the fact that these drugs are in part dependent on functional LPL and therefore lack of response to these drugs serves as a surrogate for low LPL activity.

The standard of care for FCS consists of extreme dietary fat restriction to less than 20 grams of fat per day, the equivalent of approximately 1 tablespoon of olive oil or half of an avocado and also avoidance of alcohol.

Even with strict adherence to this challenging regimen, triglyceride levels are not typically lowered sufficiently to reduce the risk of pancreatitis in many patients, leaving individuals at risk for pancreatitis and other
signs and symptoms of this disease.

To summarize, FCS is an ultra rare inherited life-threatening metabolic disorder of triglyceride metabolism. FCS can be clinically differentiated from the larger group of patients with chylomicronemia. Currently, there are no effective therapies for lowering triglyceride levels in patients with FCS.

As a result, most patients with FCS remain at high risk for pancreatitis. Thus patients with FCS have a clear unmet need for effective and sustained triglyceride-lowering treatments to reduce the disease burden.

In view of the high risk and severity of pancreatitis in patients with FCS, Dr. Freedman will expand on this potentially life-threatening consequence. Thank you.

**Applicant Presentation – Steve Freedman**

DR. FREEDMAN: Good morning. My name is Dr. Steve Freedman. I'm professor of medicine at Harvard Medical School and director of the Pancreas Center at Beth Israel Deaconess Medical Center in
Boston, one of the largest pancreatic referral centers in North America.

I treat patients of all ages with pancreatitis caused by hypertriglyceridemia as well as cystic fibrosis, as I'm also affiliated with Boston Children's Hospital. I'm here today to provide additional insights into hypertriglyceridemia-induced pancreatitis as it pertains to FCS.

Approximately 70 percent of patients with FCS will develop pancreatitis as a result of their chylomicronemia, hypertriglyceridemia, with half of these individuals having anywhere from 2 to 96 episodes in their lifetime. In addition, the morbidity and mortality of pancreatitis associated with hypertriglyceridemia is greater than from other etiologies.

Correlation between increased triglyceride levels and the increased risk of pancreatitis is well established. Therefore, one of the major goals for patients with FCS is to reduce their triglyceride level in order to reduce the
associated risk of pancreatitis.

Since there's little information on pancreatitis in FCS due to the rarity of this disease, I'll focus the majority of this presentation on the data from patients with severe hypertriglyceridemia. I'll begin with a brief overview of pancreatitis and then discuss the relationship to triglyceride levels.

Pancreatitis is a serious and potentially life-threatening condition. It's characterized by severe upper abdominal pain with nausea, vomiting, and fever. It's usually an acute event, but with repeated bouts, chronic pancreatitis can occur, which is an unrelenting, searing, daily pain that worsens with every meal.

Mild cases resolve within 2 to 4 days, but in approximately 20 percent of patients, complications develop as a result of necrotizing pancreatitis, leading to multiorgan failure, which consists of acute respiratory distress syndrome, renal failure, and/or shock.

In addition, infection can develop and
 pseudocysts may form over time. Mortality can be quite high, ranging from about 3 percent in milder cases to 30 percent in severe cases. The risk of pancreatitis as well as severity increases along a continuum of increasing triglyceride levels.

Shown here are data from a U.S. claims database review of over 40,000 adults with triglyceride levels above 500 milligrams per deciliter. The incidence of pancreatitis over an average 825-day observation period is shown as a function of follow-up triglyceride levels.

The analysis shows that the risk of acute pancreatitis increases proportionally with increasing triglyceride levels. Importantly, this study showed that lowering triglycerides from the starting value of greater than 500 could reduce the pancreatitis risk.

If we examine this risk at higher triglyceride levels, other studies have shown that triglyceride values above 1,000 milligrams per deciliter, approximately 5 percent of individuals will develop acute pancreatitis over their
lifetime.

This increases to 10 to 20 percent with triglyceride values above 2,000. Conversely, reducing triglycerides decreases the risk of pancreatitis. In general, the recommendations are to reduce triglyceride levels below 1,000 milligrams per deciliter to reduce the risk.

So now, let's look at the severity of pancreatitis as a function of triglyceride levels. Nawaz and colleagues conducted a prospective observational study evaluating outcomes in 201 patients hospitalized with acute pancreatitis, with serum triglyceride levels measured within the first 72 hours of admission.

Shown here is the proportion of patients with organ failure as a function of initial triglyceride level, multi-organ failure persisting beyond 48 hours defines severe pancreatitis in the Atlanta criteria and is the most common cause of death in these patients.

As you can see, there's a clear concentration-dependent relationship between
triglyceride levels and persistent organ failure. Nearly half of the patients with triglyceride values greater than 1,000 had organ failure in this study.

Additional data from the Nawaz study confirmed that higher triglyceride levels are associated with more severe disease. 60 percent of patients with very high triglyceride values needed to be in the ICU compared to 23 percent with normal triglyceride values.

Fifty percent of patients with triglyceride over 1,000 had necrosis and had a prolonged hospital stay. Mortality in this study was 8 percent compared to 3 percent with normal triglyceride values on admission.

That's the patient's first hospitalization for hypertriglyceridemia-induced pancreatitis, maybe their last due to death.

In closing, pancreatitis due to underlying hypertriglyceridemia is a much more severe form of pancreatitis as compared to other etiologies. Both the morbidity, including multiorgan failure and
mortality, are increased.

Among the many clinical manifestations of FCS, pancreatitis is the most serious. Unfortunately, even the first instance of pancreatitis may be fatal. The suffering of these patients cannot be estimated when meals are a frequent trigger of abdominal pain and patients live in constant fear that one of these bouts will put them in the hospital and likely in the intensive care unit.

Unfortunately, this is a typical scenario for these patients. All available data indicate that the risk of pancreatitis increases and decreases as a continuum related to triglyceride levels. Therefore, an effective medication to substantially lower triglycerides would allow patients to achieve triglyceride levels below those associated with an elevated pancreatitis risk.

Thank you. I'll now return the podium to Dr. O'Dea.

Applicant Presentation – Louis O'Dea

DR. O'DEA: Thank you, Dr. Freedman. I'd
like to discuss the efficacy data supporting the
application of volanesorsen in this proposed
indication. The data show that patients treated
with volanesorsen achieved statistically
significant and clinically meaningful sustained
reductions in fasting triglyceride levels.

Importantly, this efficacy was consistent
across clinical studies. Here is an overview of
the volanesorsen clinical development program. For
an ultra rare disease, this is a sizeable dataset
of almost 400 patients and subjects, of whom
312 received volanesorsen and 84 of these were
patients with FCS.

This is the largest collection of clinical
data in patients with FCS to date. The program
supporting the application includes 2 phase 1
studies conducted in healthy volunteers and 2 phase
2 studies conducted in patients with
hypertriglyceridemia.

The primary data for the FCS indication are
based on the phase 3 study CS6, which will be the
focus of today's presentation. Study CS7, an open-
label extension study in patients with FCS, provides further information on long-term triglyceride reductions. Patients with FCS in this study rolled over from CS6, or study CS16, or were recruited as naïve patients.

CS16 provides further efficacy and safety data of volanesorsen for triglyceride reduction in severely hypertriglyceridemic patients and also on pancreatitis risk reduction.

These patients allowed for increased exposure that would not be possible if we studied patients with FCS alone due to the ultra rare nature of this disease.

Let me start by briefly describing our dose-finding studies, CS2. CS2 was a phase 2 placebo-controlled dose-response study conducted in 85 moderately hypertriglyceridemic subjects to evaluate the effects of volanesorsen on fasting apoC-III and on triglyceride levels.

We studied three doses, 100, 200, and 300 milligrams. And patients were required to have baseline triglyceride levels between 440 and
2,000 milligrams per deciliter. The study included patients on volanesorsen alone and a cohort of patients taking fibrates.

Finally, 3 genetically confirmed patients with FCS were enrolled in the study and received 300 milligrams of volanesorsen for 3 months. This study demonstrated a clearer dose-dependent reduction in triglycerides. Here, you see placebo in orange compared to the three tested doses of volanesorsen with dosing going through day 85, as shown in the shaded area.

At baseline, the mean triglyceride level was 581 milligrams per deciliter. At 3 months, volanesorsen, 300 milligrams, achieved an 80 percent reduction in fasting apoC-III and, as you can see, a 71 percent mean reduction in triglycerides.

The effect was sustained for at least another 3 months. After dosing stopped, triglyceride levels slowly returned to baseline, reflecting the long effective half-life of volanesorsen.
Among the 3 patients with FCS studied with volanesorsen, the triglyceride reduction at 3 months was 64 percent.

Therefore, this study showed clinically meaningful reductions in triglyceride with 300 milligrams of volanesorsen. In addition, it confirmed that the apoC-III pathway was a target for the treatment of patients with FCS who have similar degrees of triglyceride reduction as normal subjects.

Study CS2 identified no dose-limiting toxicities. And while some dose-dependent platelet reductions were observed, the group mean values remained within the normal range. No platelet-related serious adverse events or discontinuations occurred.

This safety profile supported taking the 300-milligram dose into our phase 3 development program, in particular considering the extreme elevations of triglycerides in patients with FCS.

Let's now review our pivotal phase 3 study, CS6, conducted in patients with FCS. CS6 was a
phase 3 double-blind randomized placebo-controlled 12-month study. The study comprised a screening period of up to 8 weeks, which included a diet stabilization period of at least 6 weeks.

Subsequently, patients were randomized 1:1 to receive subcutaneous injections of either volanesorsen, 300 milligrams, once weekly or a matching volume of placebo. Following completion of the 52-week treatment phase, patients could elect to enroll in the open-label extension study, CS7. Patients not participating in the open-label extension entered a 13-week post-treatment follow-up period.

Inclusion criteria required that patients be 18 years of age or older and to have agreed to a very restrictive fat diet of 20 grams or more per day, which is the current standard of care.

Patients were also required to have a fasting triglyceride of greater than or equal to 750 milligrams per deciliter and to have either positive genetic or lipoprotein lipase functional testing, documented pre-randomization.
Most patients were also retested for genetic markers on study. This is the population for which we are pursuing approval. Finally, a majority of patients were to have prior pancreatitis.

The agreed-upon primary endpoint in study CS6 was the percent change in fasting triglyceride levels from baseline to 3 months, which is sufficient to realize the full effect of triglyceride-lowering therapies.

All triglyceride endpoints are based on two values, separated by 1 week. The full analysis set included all patients who were randomized, received at least 1 dose of study drug, and had a baseline plasma triglyceride assessment.

Various imputation methods were used for missing data. We minimized missing data by asking that patients continue to attend scheduled study milestone visits even if they discontinued study medication.

Patients who discontinued early were also followed for safety, including cases of pancreatitis, achieving similar durations of
observation for both volanesorsen and placebo
groups. That said, all patients had triglyceride
values at month 3, so the primary endpoint retained
the full analysis set with all observed values.

Imputation methods for months 6 and 12 again
included multiple imputations methods as well as a
post hoc analysis of missing not at random.

So turning to our study demographics, these
study demographics were balanced between arms.
Patient population was relatively young with an age
range of 20 to 75. Patients were diagnosed on
average at age 27. The genders were approximately
equally represented in each arm and patients had a
BMI of around 25.

Their body weight was 70 kilos on average
and the majority of patients were white. Baseline
mean triglyceride levels were markedly elevated
with mean levels around 2,200 milligrams per
deciliter, close to 20 times the normal value.

It's important to remember that these
baseline values reflect levels even after 6 to
8 weeks of diet control and education. More than
90 percent of patients had triglyceride values greater than 750 at study start.

Per the entry criteria, FCS diagnosis was confirmed genetically or by a lipoprotein lipase assay. As expected, most patients had a history of acute pancreatitis. 29 percent of patients were also on lipid-lowering agents and still had very high levels of triglycerides.

In study CS6, 58 percent of volanesorsen-treated patients and 94 percent of placebo-treated patients completed 12 months of study treatment. 14 patients discontinued treatment with volanesorsen. 4 of these were voluntary withdrawals. 9 were related to adverse events. 5 of these in turn were adverse events of platelet count reductions.

Moving to the primary results, study CS6 met its primary endpoint of present reduction in triglycerides at 3 months compared to placebo. Volanesorsen-treated patients achieved a mean reduction in triglycerides of 94 percent compared to placebo and 77 percent compared to their own
baseline.

This is statistically significant when compared to placebo. This result reflects a mean reduction in triglycerides of about 1,600 milligrams per deciliter from baseline and brings patients to a new average of 590 milligrams per deciliter at month 3.

So next, we'll present the results of the primary endpoint by individual patient. The X axis represents individual patients from study CS6. The Y axis shows triglyceride values. The horizontal line at 750 represents the triglyceride level at which chylomicrons form in the blood and therefore are responder threshold.

Let me walk you through the results of 1 patient before presenting all data. The blue circle represents the baseline triglyceride value of 3,690 for this patient. At month 3, this patient's triglycerides were reduced to 460 milligrams per deciliter.

Here are the rest of the results from the volanesorsen-treated patients, ordered based on
final triglyceride values. By month 3, all
patients had a decrease in triglycerides from
baseline and 77 percent of the patients achieved
triglyceride values below 750.

The data in orange represent the placebo,
with changes in both directions from baseline
values. A notable difference between treatment
groups underscores both the pronounced efficacy and
the high response rate to volanesorsen.

So moving to the secondary endpoint results,
as Dr. Freedman stated, there are risk thresholds
for the serious complications of FCS. Consistent
with previous FCS development programs, 750
milligrams per deciliter was pre-specified as the
responder threshold, as it represents an important
risk threshold for pancreatitis and reflects the
triglyceride level at which chylomicrons
predominate in the circulation.

Seventy-seven percent of treated patients
achieved that level compared to 10 percent of
placebo patients. We also evaluated other risk
thresholds commonly found in the literature;
1,000 milligrams per deciliter, 880 milligrams per
decimal, which is more widely applied in Europe,
and 500 milligrams per deciliter, which is an
important level for risk of pancreatitis since it
represents a 2.5-fold risk for patients with normal
triglyceride values.

Independent of the threshold assessed,
patients treated with volanesorsen achieved a
statistically significant reduction in risk levels.

So moving to long-term efficacy data, we
continue to see clinically meaningful and
statistically significant reductions in
triglycerides at the pre-specified 6- and 12-month
time points. These data include all 33 patients in
the full analysis set at each time point, with a
multiple imputation method use for missing data at
6 and 12 months.

This means that, even if patients
discontinued early or went off treatment after
month 3, a value was imputed at months 6 and 12.
As a reminder, dose adjustments were made after
month 3 if needed to minimize platelet count
reductions.

To illustrate the contribution of these reductions or discontinuations, let me turn to the next slide. This graphic provides detail on persistence of efficacy, taking into account dose adjustments. As you can see, patients who continued without dose adjustment show consistent sustained response to volanesorsen.

Patients who had a dose adjustment retained most of the triglyceride reductions through 52 weeks. Patients who discontinued prematurely contributed to some loss of efficacy within the full analysis set at 52 weeks.

As expected, the placebo group showed no overall improvement over time. It's important to note that, for patients who completed 52 weeks, significant triglyceride reduction was maintained.

Using this dataset, we evaluated factors that might predict the need for dose adjustment, body weight was the strongest predictor, leading us to propose weight-based dose adjustment post-approval.
Moving to the pre-specified secondary endpoint of maximum intensity of abdominal pain, it was not a significant difference between treatment groups and reported events nor in the distribution of event severity. Abdominal pain is an important part of FCS and is confirmed by patient surveys.

Our phase 3 study finding likely reflects limitations of the measurement tool that we use. So we're working to develop a more appropriate validated pain assessment tool for patients with FCS.

So next, I'll turn to additional pre-specified exploratory endpoints. Pancreatitis, in association with abdominal pain, was a pre-specified endpoint in the study protocol and statistical plan. In the absence of an effect on pain, we looked at events of pancreatitis alone.

Serious adverse events of pancreatitis were adjudicated by an independent medical committee. On treatment, 1 volanesorsen-treated patient suffered an event of pancreatitis and 3 placebo-treated patients suffered 4 events of pancreatitis.
So in such a rare disease with small patient numbers and the reported background frequency of pancreatitis, the significant impact on pancreatitis would not have been predicted. Nonetheless, these numbers do suggest a therapeutic effect.

An additional exploratory analysis looked at patients with more than one event of pancreatitis in the past 5 years. We noted that patients may expect an attack of pancreatitis every 4 to 5 years. So we looked at patients with more than these frequency to ascertain if volanesorsen has a protective effect.

There were 24 events in 7 volanesorsen patients over the 5 years prior to the study and none of these patients experienced pancreatitis during the course of treatment. Among the placebo patients, there were 17 prior events and 4 patients.

By contrast, to the improvement seen on volanesorsen, 3 placebo patients experienced 4 events of pancreatitis during the study period.
In the absence of a validated tool, quality of life tool for patients with FCS, we use two general questionnaires, the EQ-5D and the SF-36.

While these tools are commonly used in clinical trials, they've not been validated for patients with FCS. No differences were observed in the quality of life between drug- and placebo-treated patients used in these measures.

So we understand that enhancing the quality of life for patients with FCS is an essential component in managing the disease. And therefore, we have been committed to develop an FCS-specific quality of life measure from early on in this program.

Our early work has been published and has become a reference in the field. Further data I'd like to briefly review are from the open-label extension study, CS7. This study is a phase 3 open-label clinical trial designed to evaluate both the safety and efficacy of extended treatment with volanesorsen in patients with FCS.

Patients in CS7 included continuing
volanesorsen-treated patients from studies CS6 and CS16 as well as treatment-naïve patients made up of placebo patients from these studies and newly identified patients with FCS. The majority of eligible patients chose to continue treatment.

New patients with FCS who had not participated in CS6 or CS16 had to meet the eligibility criteria of CS6 to be enrolled. CS7 allowed treatment for up to 24 months after the initial 12 months in study CS6.

Let's look at the sustainability of effect for patients moving from CS6 to CS7. Volanesorsen treatment continues to provide efficacy for at least 24 months as patients from CS6 progress into CS7. We present here the longitudinal data of CS7 with the 12 months of earlier participation in study CS6 shown in the shaded area.

The CS7 study continues, but these data are taken from the last formal analysis and therefore not all current patients are included in the later time points.

I'll now briefly walk through the additional
data which are derived from study CS16 in patients with severe hypertriglyceridemia. Although we are not seeking an indication for patients with severe hypertriglyceridemia, the triglyceride levels in this population are well above the upper limit of normal while on standard treatment.

We therefore consider patients with severe hypertriglyceridemia to be a relevant population to better understand the safety and pharmacology of volanesorsen, in particular since as Dr. Freedman indicated they have an increased background risk of pancreatitis.

In study CS16, volanesorsen caused significantly greater triglyceride reductions in the volanesorsen group relative to placebo. The difference from placebo and percent change in triglycerides was 71 percent, consistent with the efficacy observed in patients with FCS.

Adjudicated pancreatitis events occurred in 3 patients in the placebo group compared with no patients in the volanesorsen group.

To further evaluate the potential effect on
the risk of pancreatitis, we conducted informative post hoc analyses of all patients with FCS and patients with hypertriglyceridemia. Among patients with FCS from study CS6 and study CS16, we observed similar distributions of pancreatitis events.

Overall, there were 6 events in 4 placebo patients and 1 event in a volanesorsen patient. Each individual study and the group of all patients with FCS from both studies show point estimates for risk of pancreatitis well below 1.

Importantly, the results from the FCS and hypertriglyceridemic populations were consistent. So to conclude, volanesorsen treatment leads to clinically meaningful and statistically significant reductions in triglycerides of 94 percent relative to placebo. These reductions in triglycerides were sustained over time.

The degree of triglyceride reduction should reduce the risk of pancreatitis and point estimates for pancreatitis risk support this potential. In fact, in all exploratory assessments of pancreatitis, volanesorsen consistently showed a
numeric benefit.

Given the severity of this disease and the absence of alternative effective therapy, these substantial reductions in triglycerides, which drive the symptoms and complications of this disease are meaningful and medically important to these patients.

Overall, these data indicate that volanesorsen could be the first effective therapy to treat patients with FCS. So with that, I'll turn the podium over to my colleague, Dr. Walter Singleton, who's been involved in this program since its inception.

Applicant Presentation - Walter Singleton

DR. SINGLETON: Thank you, Dr. O'Dea. I'm Walter Singleton, former chief medical officer for Ionis Pharmaceuticals. Our data demonstrate that the safety profile of volanesorsen is well understood with risks that could be monitored and managed.

So let me start by reviewing the volanesorsen exposure throughout out our phase 2
and phase 3 programs. The clinical trial program included 189 patients who received treatment with the 300-milligram dose of volanesorsen at the time of data cut-off for this review.

And these totals include patients on volanesorsen in the controlled phase 2 and 3 studies, patients on placebo in the controlled trials who then went on to receive volanesorsen in the open-label extension study, CS7, and a small number of new patients entering CS7 de novo. 150 of these patients were treated for at least 3 months, 74 for 6 months or more, and 26 for more than a year.

Of these, 84 are patients with familial chylomicronemia syndrome, with the majority from the pivotal CS6 study. And of these, 48 have been treated for 6 months or longer and 26 for over a year at the time of data cut-off. So as you will appreciate, this represents a substantial database for a study in such a rare population.

These data are from the pivotal study CS6 in patients with FCS. Together with supporting data
from CS6 to provide a larger safety dataset. The numbers of adverse events were similar between active treatment and placebo groups.

In CS6, there were 7 of 33 patients who had a serious adverse event in the volanesorsen arm and 5 of 33 in the placebo arm. And there were no deaths across the studies.

The overall rate of discontinuation was in the range of 20 to 27 percent in patients on volanesorsen and between 0 and 8 percent in patients on placebo.

The most common reason for discontinuation in CS6 was platelet count decrease from thrombocytopenia. In addition, 2 patients also discontinued due to fatigue and one to injection site reaction.

The most common reason for discontinuation for CS16 was injection site events, but all patients who discontinued due to injection site events had events that were moderate in severity and all the other events which still occurred in a single patient in each study group.
So I would now like to focus the rest of this presentation on specific safety topics, including platelet count reductions, injection site reactions, immunogenicity, and renal and hepatic events.

So first focusing on platelet changes, the first thing to note is that 55 percent of patients with FCS and CS6 on volanesorsen, 18 were less than 100,000 per cubic millimeter on treatment versus none on placebo. In CS16, 9 of the 75 patients with volanesorsen had a platelet count below 100 compared with 1 of 38 patients in the placebo group.

However, breaking these into severity categories, it's clear that the more severe reductions in both studies were observed only in the volanesorsen-treated patients with 2 patients with FCS dropping below 25,000.

Now, this graph shows mean platelet count by patient study week. At the start of the CS6 study, based on phase 2 data, platelets were monitored every six weeks. Now, changes in platelet count in
most volanesorsen patients were gradual declines and stabilized over time, with platelet count generally remaining above 100,000.

Severe thrombocytopenia, however, occurred in 3 patients, shown here in the red triangles. And you will note that the latter two events occurred in May of 2016, within a three-day period. And this is what triggered the enhanced monitoring that you'll hear about later.

All 3 cases of severe thrombocytopenia occurred on the original protocol monitoring of every 6 weeks. And as a result of this, the algorithm was revised to increase monitoring to every 2 weeks in order to identify potential platelet reductions at the earliest possible stage.

Over the course of the entire clinical program, 9 patients had platelet count reductions below 50,000 per cubic millimeter. It's important to note that all patients shown here recovered and there were no major bleeding events.

Four of these patients had reductions in platelet monitoring even after the enhanced
monitoring program had been implemented. And in
3 of the 4 events, either the monitoring interval
or dose adjustment were not carried out in
accordance with the algorithm.

We investigated all these events and
considered the causes when improving our algorithm
and designing our risk management program.

For platelet reductions that occurred during
the enhanced monitoring, treatment was immediately
discontinued. Platelet levels recovered out of the
higher risk zone in between 3 and 6 days and
returned to normal in approximately 2 weeks or
less.

As is the case with many medications given
by subcutaneous injection, adverse events at the
injection site are frequent and as shown here are
seen in both groups. The majority of these adverse
events were mild. None were severe. And
importantly, they led to discontinuation in only 1
patient with FCS in the CS6 study and the incidence
appeared to decrease over time.

Turning now to immunogenicity, overall,
antidrug antibodies were detected in 11 CS6 patients on volanesorsen and in 1 placebo patient. The median time to onset of antibodies was 180 days. And these were generally present at low titers.

Importantly, triglyceride reductions were similar between antidrug antibody positive and negative patients. And there was no association between antidrug antibody status and the incidence of injection site reactions, constitutional symptoms, or platelet reductions.

Hypersensitivity events occurred in patients without FCS in 2 cases. 2 cases occurred during the development program. One was a report of serum sickness in study CS16. Antidrug and anti-DNA antibodies were positive in this patient and the patient was treated with steroids and symptoms resolve rapidly.

The second patient experienced a serious adverse event of anaphylactic reaction. The patient was treated with epinephrine and steroids and the event resolved on the next day. And again,
antidrug antibodies were present 6 weeks prior to this event.

Moving now to renal tolerability, there were 4 adverse events related to renal function in the volanesorsen group, but none of these events were serious, all of them resolved, and none resulted in study discontinuation.

No patient in CS6 discontinued drug due to a hepatic-related event and no patient treated with volanesorsen met Hy's law. One placebo-treated patient did in fact meet Hy's law criteria.

Now, adverse events related to hepatic function occurred in both treatment groups without a clear relationship to volanesorsen treatment.

In conclusion, the safety profile of volanesorsen is well understood. The principal safety concern is thrombocytopenia. Platelet reductions occurred over several weeks and were reversible. And there were no serious bleeding events. With monitoring every other week and dose reductions, platelet levels were managed and there were no further dropouts in CS6. And we continued
to see improved patient retention in the open-label study CS7.

From our experience in treating these patients, we have developed a comprehensive risk management program to further ensure safe use post-approval. We remain committed to furthering our knowledge of the safety profile of volanesorsen and appropriately managing identified and potential risks.

Thank you. Dr. Stevenson will now provide a more detailed discussion of the risk management program.

Applicant Presentation – Michael Stevenson

DR. STEVENSON: Thank you, Dr. Singleton. Good morning. My name is Mike Stevenson and I'm the vice president of global medical affairs at Akcea Therapeutics. Let me now turn to our comprehensive and integrated risk management program.

Our risk management program focuses on thrombocytopenia, which is the primary identified risk of volanesorsen. We have consulted with FDA
on our proposed REMS program and have designed measures to promote the safe use of volanesorsen in patients with FCS.

As Dr. O'Dea mentioned, our comprehensive risk management program consists of these 5 elements, labeling, REMS with elements to assure safe use or ETASU, enhanced pharmacovigilance, a patient support program, and a treatment registry study.

Let me review these elements in greater detail. Our labeling includes a modification to our monitoring and dosing algorithm used in the phase 3 clinical trial as well as other safety elements.

These include weight-based dosing, a patient medication guide, and early threshold for dose pause. In this algorithm, all patients, platelets are monitored at least every 2 weeks. Reductions in platelet counts may trigger changes in either dose regimen, monitoring frequency, or both, as outlined in this table.

Patients with normal platelet levels who
weighed less than 70 kilograms will start with weekly dosing for 3 months and then transition to dosing every other week. Those who weigh more than 70 kilograms will dose weekly. If platelets drop below 100,000, volanesorsen dose frequency changes to every other week and platelet monitoring is increased.

Declines below 75,000. Trigger a dose pause and twice weekly platelet monitoring, whereas values below 50,000 trigger expedited lab turnaround time, rather, to enable daily platelet monitoring with dose pause until platelet count increases above 100,000.

If platelets fall below 25,000, we recommend discontinuation of volanesorsen. The REMS and the patient support program are designed to support the adherence of this algorithm post-approval. Furthermore, we will implement elements to assure safe use as part of the REMS.

In collaboration with FDA, we based our proposed REMS on an existing program. All patients diagnosed with FCS, physicians, and especially
pharmacy must enroll in our program. No volanesorsen will be administered if any of these elements is absent.

First, before they can prescribe or dispense volanesorsen, all physicians and the specialty pharmacy will be certified. This will involve training on the risk of thrombocytopenia, platelet monitoring requirements, and adjusting the volanesorsen regimen in accordance with the algorithm.

Knowledge of these topics will be assessed through a certification examination. Before starting treatment, prescribers will counsel patients on the benefit-risk profile, including how to recognize signs of abnormal bleeding.

All volanesorsen-treated patients will be registered to allow complete and close follow-through of the requirements of the REMS program. Finally, during treatment, prescribers will document the safety of each patient by submitted patient status forms every 90 days in order to continue therapy. Pharmacies will have to verify
prescriber certification and patient authorization. Dispensing will be limited to a 1-month supply. An additional component of the risk management program is enhanced pharmacovigilance. This program is intended to provide early detection of thrombocytopenia and to identify any trends in platelet counts.

We will actively follow up on reported cases with targeted adverse event questionnaires and periodic aggregated safety reports will be submitted to FDA. The pharmacovigilance system will also monitor events, including injection site reactions hypersensitivity, hepatic, and renal-related safety.

A key component of the risk management program is the patient support program or the PSP. The PSP supports patient by facilitating compliance with the monitoring. The cornerstone of this program is a dedicated team of nurse case managers who will focus on individualized patient services.

These will include scheduling blood draws either at labs or through mobile phlebotomy, which
enables blood draws at home, work, or other venues
convenient for the patient with FCS.

In addition, the nurse case managers will
provide supplemental patient education, compliance,
and adherence tools. Further, the PSP will employ
a multifaceted alert system for healthcare
practitioners, specialty pharmacy, and patients
based on pre-specified platelet thresholds per
product labeling.

Let me walk you through some of the aspects
of the prescription generation as well as these
alert systems to demonstrate some of the program's
safeguards. Prescribers in the specialty pharmacy
must be certified prior to either the authorized
writing or dispensing of a volanesorsen
prescription.

If the prescriber does not attest to the
diagnosis of FCS or to patients being at least 18
years of age, no drug is shipped. Likewise, if the
prescriber or pharmacy isn't certified, no drug is
shipped. If a patient is diagnosed with FCS, they
will be registered into the REMS program. Failure
to register, no drug is shipped.

The patient receives their blood draw either at a lab or with mobile phlebotomy. If a patient misses a subsequent blood draw, the prescriber will be contacted before drug is dispensed. The results are sent to the prescriber, specialty pharmacy, patient, and nurse case manager and analyzed. And a specialty pharmacy verifies each order.

If the platelet count is normal, a 1-month supply of volanesorsen is shipped to the patient. Upon administration, the monitoring continues per the dosing algorithm. If the patient count falls below a threshold value, the prescriber, pharmacy, case manager, and patient receive alerts from the lab. The dose and monitoring will then be adjusted according to the proposed algorithm.

An additional element, finally, beyond the REMS program will be a post-commercialization global registry study to follow more than 100 patients.

This study will assess trends, signals, and potential adverse events, most notably
thrombocytopenia, and further characterize the monitoring and dosing algorithm. This registry study will also aim to characterize the longitudinal safety of volanesorsen as well as longitudinal effects on triglycerides and pancreatitis.

In summary, we have proposed multiple activities with checkpoints to manage patient safety while making platelet monitoring and compliance as straightforward as possible. Given the high unmet medical need of patients with FCS and the urgency to provide a specific treatment, the proposed comprehensive and integrated risk management program will support a favorable benefit-risk profile post-approval.

Thank you, and Dr. Baum will now conclude the presentation with his clinical perspective.

**Applicant Presentation – Seth Baum**

DR. BAUM: Thank you. I am Seth Baum, current president of the American Society for Preventive Cardiology, affiliate clinical professor at the Schmidt College of Medicine and a practicing
clinical lipidologist and preventive cardiologist.

Today, we have seen compelling data from the sponsors and other experts. We have heard that familial chylomicronemia syndrome is an ultra rare disease, conferring a 70 to 80 percent lifetime pancreatitis risk. We know that the higher the triglycerides, the greater the risk of severe pancreatitis.

With each pancreatitis episode, patients with FCS have a 6 percent risk of dying. The clinical trial data prove that volanesorsen can significantly lower triglycerides in patients with no therapeutic options. No triglyceride-lowering medicine is effective or approved in FCS, leaving us, the treating physicians and the patients, with no solutions.

The data also identify the thrombocytopenia risk. In response to this, the sponsor has created a comprehensive risk management strategy, including the prescribing doctor, a specially trained nurse, a single central laboratory, a single dispensing specialty pharmacy, and the patient.
Additionally, the REMS was developed in collaboration with FDA. The aim is to reduce the risk of severe thrombocytopenia. In my view, the sponsor has created a practical program for the clinical setting. In fact, I have already seen this work when treating my own patients. We readily adhere to the algorithm.

The program has even included a robust registry. It will inform us about this ultra rare disease and help keep patients safe while affording them the opportunity to receive this beneficial drug.

Currently, I have one patient with FCS on drug in CS7 and 3 patients with FCS eagerly awaiting entry into the volanesorsen early access program. Eagerly is an understatement. They are literally begging to get in.

A 59-year-old woman with multiple hospitalizations and procedures for pancreatitis, a 60-year-old man with diabetes as a consequence of such severe pancreatitis, and a 47-year-old woman with a persistent triglyceride level between 10,000
and 12,000.

All fully understand the risks of volanesorsen, yet can't wait to be started on the medication. That is because they know and live the risk of not being on volanesorsen. They understand that each episode of pancreatitis can be fatal.

This is not hyperbole. I am not exaggerating. In fact, I am probably understating their anguish and risk. They live in constant fear of the next inevitable pancreatitis attack and its associated risk of death. Volanesorsen is their only option.

When I practiced interventional cardiology, I'd constantly assess the risk-benefit relationships of some of the most serious interventions. With that experience in mind, now as a lipidologist and preventive cardiologist who treats patients with FCS, I am confident that volanesorsen should be approved.

We have seen the data. We know the risks and the benefits. We know that we need to monitor the risks and we have the support system to do so.
Most importantly, this small group of patients needs a therapy to lower their triglycerides.

Now, we can give them that opportunity by recommending approval to the FDA. Thank you.

Dr. O'Dea will now return to take your questions.

**Clarifying Questions to Applicant**

DR. WILSON: Thank you very much. So the next step that was just referred to is clarifying questions for Akcea. Please remember, for those posing questions, to state your name for the record before you speak and please direct your questions to a specific presenter.

And then once you're finished with your microphone, push the red light off, so Dr. O'Dea, yes, go ahead. Do we have a question? Dr. Burman, go ahead.

DR. BURMAN: Thank you. Thank you for that nice presentation. My question, though, for clarification a little bit is for Dr. Singleton. And my question is, if I quoted him correctly, he said the safety profile of the agent is well understood.
But I'd like his further comments on, number one, the mechanism by which he thinks are as proven that the platelet count is low, whether there's any effective on vascular endothelium from this agent, and I didn't see any results on platelet function, just platelet numbers.

It appeared that some of the platelet decreases were idiosyncratic in nature and couldn't be predicted. Thank you.

DR. O'DEA: So Dr. Burman, if you wouldn't mind, I'll ask Dr. Scott Henry to take that. He's done a lot of our primary research to understand this question. Dr. Henry is head of non-clinical development at Ionis.

DR. HENRY: Yes, is this on? Scott Henry, non-clinical at Ionis Pharmaceuticals. So we've done quite a bit to study the effect on platelet function specifically, including actually -- and a lot of this has happened in our animal models, where we can dig into this a little bit more.

So we've actually treated monkeys for a period of time, 3 months, tested their platelet
function by traditional platelet aggregometry or PFA-100, which is basically a coagulation test and seeing no effect on platelet function.

Also in vitro we see no direct platelet activation either in monkey or human platelets and using related compounds, no impairment of the platelet response to ADP or collagen normal stimulants, also no increase in bleeding time.

To your question about other mechanisms, essentially we've ruled out an effect on either bone marrow production or other sort of microangiopathy, thrombosis endpoints, and that includes essentially excluding an effect on endothelium.

We see no change in Von Willebrand factor. So again, we've excluded a number of very important mechanisms. Either make a karyocyte number or function and thrombosis or endothelial interactions. So that's the status of our investigation at this point.

DR. WILSON: Dr. Newman?

DR. NEWMAN: My name is Dr. Connie Newman.
I'm from NYU and I have a question about the baseline levels of triglycerides in the patients in CS6. I understand that these patients were on diet, but I was still very surprised to see there were levels in the 300s.

Usually, patients with familial chylomicronemia syndrome have triglyceride levels of 2,000 or above as well as clinical symptoms. So do you have any data on the triglyceride levels in these patients before they were treated with diet?

DR. O'DEA: So if I could clarify, the baseline triglyceride levels were 2,200 on average in the patients after their 6 weeks of diet introduction. Our patients, I think we mentioned, were diagnosed in general in their 20s on average. At the time they came to the study, they were in their 40s.

DR. NEWMAN: I'm looking at CO-44, where the circles show the baseline levels in individual patients, so I'm just talking about individual patients.

DR. O'DEA: So the blue circles are the
baseline at entry.

DR. NEWMAN: Right.

DR. O'DEA: The black squares are the final 3-month data. Right.

DR. NEWMAN: Right. And some of the blue circles are very low.

DR. O'DEA: Yes. There are two circles, which are below 750. Now, at the time the patients were screened, all of the patients were at 750. Some of the patients subsequently had slightly lower values as they entered the study. But the mean for the population was 2,200.

DR. NEWMAN: I have a question for Dr. Rader. In your experience, what level of triglycerides do patients with familial chylomicronemia syndrome have? Because the literature says 2,000 and above.

DR. RADER: Patients with FCS have chylomicronemia, which generally starts to appear over about 750 milligrams per deciliter. Certainly many of these patients have even much higher levels of triglycerides. It's absolutely true.
These patients in this trial were placed on a very low fat diet, which adherence to is relatively variable. And there's also variability among FCS patients in terms of their response to diet.

So I would suggest one possibility would be those few individuals who had appropriate triglycerides to get into the study, but then were placed on the very low fat diet were adherent and happened to have at least enough of a response to bring their baseline triglycerides down to the levels that we saw in that slide.

DR. NEWMAN: Thank you. Thank you.

DR. WILSON: Dr. Morrato?

DR. MORRATO: Thank you. Dr. Morrato. My question is for Dr. Stevenson and the risk management program. And I'm just trying to understand a little bit, two points. One is the scientific evidence in support of the monitoring and evidence in terms of burden to the healthcare system. So are you able to answer?

So my question is, we have a lot of examples
in medicine in which you have rare adverse events
that we say, let's go ahead and monitor them on a
certain frequency.

  DR. O'DEA: Right.

  DR. MORRATO: It sounds good on paper, but
there's really little evidence that would say that,
that excess monitoring is going to have a return on
that investment so to speak. So if you look at
slide CO-78, where you have your proposed weight
and monitoring recommendation, what is the
scientific evidence in support of this
recommendation?

  DR. O'DEA: So of course, our evidence is
empirical. We did not --

  DR. MORRATO: Based on 33 patients? So tell
me, I couldn't find a good description in the
briefing documents, exactly how you -- is this a
model, algorithm? Please explain.

  DR. O'DEA: So when we started our phase 3
program, we had a dose pause as a safety option
should we see any renal, hepatic, or platelet
changes. As we went forward in the program, as
Dr. Singleton noted, we saw two patients with an acute severe thrombocytopenia.

Caused us to make a number of changes. One of those changes was to change to allow a dose adjustment option, meaning reduced dose. So as we designed the trial with a small trial like that, multiple doses will be a challenge to find meaningful information on one versus the other. So adding a dose adjustment was considered to be a reasonable preventive step to come to, how shall I say, mitigate this risk.

The second thing we did is, we changed the range at which dose pauses happened. So previously, dose pauses happened at a higher range. We brought that up to about 75,000. So we put in two mitigations.

Now, subsequently, in that trial, we had no further platelet-associated discontinuations and subsequently had no other of course severe thrombocytopenia. So in our view, when people adhere to this, we find that we're able to limit the risk for patients.
When we completed the trial, one of the important findings we had was that, looking to try and understand both mechanistically as Dr. Henry spoke about, but also with the demographics of the treated population, could we identify demographic elements that would help us.

So we looked from a pharmacologic perspective. We looked at the rapidity of an early platelet production, like 20 percent, 30 percent, 40 percent, 50 percent in the first month at 3 months as regards whether that would be a signal that we could harness to ensure the safety of subjects.

We also looked at relationships between basal triglycerides and the risk of thrombocytopenia. We do know that the FCS proportion has a background risk of thrombocytopenia independent of any therapy. They haven't published and described.

They are a high-risk population. They may run a higher risk than other populations. We did not see the same level of thrombocytopenia in other
populations that we've studied.

So one of the insights that we had was looking at the data both in CS6, which is the FCS population, and CS16, which is non-FCS hypertriglyceridemic population, is that there is a correlation between the maximum reduction in platelets and the overall body weight.

The slope of the line in both of those studies are consistent, one with the other. So we do think the body weight related to exposure is an important factor in this.

DR. MORRATO: So what's the evidence of the threshold of 70 kilograms?

DR. O'DEA: So the evidence for 70 kilograms, I think, is WT-4 slide if you don't mind. So I just put up this slide. And again, this is after we've concluded the trial, just to be absolutely sure.

So when we look at patients who are less than 70 kilos versus patients who are greater than 70 kilos, first thing one notices is that there's a difference in exposure. The second thing one
notices is that the reduction in platelets in the
second yellow highlight is 63 percent, 62 percent,
versus 43 percent in the heavier patients, while at
the same time, looking at triglyceride response,
was still seeing a very substantial triglyceride
response of 60 percent versus 72 percent.

DR. MORRATO: So if I'm reading that
correctly, that's 11 and 8 patients?

DR. O'DEA: That's correct.

DR. MORRATO: So assuming it's practical, is
this being employed in the open label?

DR. O'DEA: So the open-label trial had
completed enrollment and so it is not -- and so our
label as you may have seen is, first 3 months, the
patients are on 300 milligrams. On a weight basis,
they automatically go to a lower dose.

So all patients have passed that point when
we made this determination. We are looking at our
early access program and it is implemented in our
early access program.

DR. MORRATO: Can I ask one question? So
the open label is evidence of someone being able to
sustain these recommendations over a long period of time. When I look at one of the slides that you presented, it looks like only 27 percent of patients are actually sustaining with this monitoring.

I know that your program was done in 20 countries. How much of that is really evidence that this is workable in the United States healthcare system?

DR. O'DEA: So if I could clarify one point, it's that we do have an 80 percent retention of patients on the open-label extension study. We had a 60 percent, you're correct, before we instituted this change.

So we do have indirect evidence that it shows some benefit having patients on this more flexible dosing regimen and also monitoring regimen. In terms of our assessment of our impact on the healthcare system, I'm not sure that we have the right people to answer that question, but perhaps from our deeper team, we can come back to you after the break.
DR. WILSON: Thank you. I'm sure we're going to come back to dosing and other discussions. So Dr. Neaton is next.

DR. NEATON: I have a question. It's really clarification. It might be helpful to pull up slide 47. So you mentioned, which I was glad to hear, that you made every attempt to get people back for triglyceride and other measurements following treatment discontinuation, as I understood it.

But if I look at this slide and the numbers below, am I interpreting it correctly that, of the 14 people who discontinued, only about half of them returned for visits for triglyceride measurement?

DR. O'DEA: So all but 6 patients continued to return for continued assessment of triglycerides.

DR. NEATON: So the numbers here, these weeks; does this correspond to what you referred to as your standard visit schedule?

DR. O'DEA: It does, but these are the on-treatment patients. This is the observed data.
The on-treatment --

DR. NEATON: The non-completers, I am assuming, are among the 14 that didn't complete the study.

DR. O'DEA: The non-completers are, yes, the 14 that didn't complete the trial. They are not represented in that data. They were represented in the previous slide, which is a full analysis set.

DR. NEATON: I guess I'm not understanding, then, because these numbers -- maybe you just need to clarify what these numbers are, then.

DR. O'DEA: Sorry. I should clarify. So as you can see, among the dose non-reduce -- perhaps the semantics are poor -- there are 6 patients who continued on 300 the whole way through, 12 patients who continued with the dose reduction, and there were 6 patients who did not reach the end of the trial, as you can see, in that graphic, all contributing to that dataset.

DR. NEATON: The legend at the top says the gray line corresponds to 14 non-completers.

DR. O'DEA: That's right.
DR. NEATON: As I look at the numbers going across, it's less than half of that at the end, right around half of that. And so basically, the people who discontinued treatment must not have been coming back for triglyceride measurement. Is that correct?

DR. O'DEA: So there are 6 patients who were coming back for regular assessments.

DR. NEATON: That's kind of what my question was.

DR. O'DEA: Yes.

DR. NEATON: So a related question concerning follow-up, and we can come back to it later; your diagnosis of pancreatitis began with a review of a serious adverse event report. Correct?

DR. O'DEA: That's correct.

DR. NEATON: That has been adjudicated.

DR. O'DEA: That's right.

DR. NEATON: So what were the criteria for reporting serious adverse events following discontinuation of therapy?

DR. O'DEA: So all serious adverse events
were reviewed by the adjudication committee, not serious adverse events alone that resulted in discontinuation. So they had a constant feed of serious adverse events.

DR. NEATON: But your protocol stipulated that, even when a person stops blinded study treatment, they were to report serious adverse events?

DR. O'DEA: That's correct. That's correct, at the milestone visits.

DR. NEATON: Did any pancreatitis events occur after discontinuation of blinded treatment?

DR. O'DEA: No. The patient on volanesorsen who had an event of pancreatitis had a triglyceride value of 300 and previously most recent injection was about 2 weeks previously.

DR. NEATON: We'll come back to this.

DR. WILSON: Dr. Everett?

DR. EVERETT: Thanks. I actually have two questions, the first on that same slide that we were just looking at. I guess it's 47. Is that right?
DR. O'DEA: That's correct.

DR. EVERETT: So specifically, this is perhaps informed by Dr. James's comments, where we have a persistent effect and you yourself made that point in your presentation. In those who did not complete, there was a persistent effect of the medication on triglycerides. And so part of me is wondering why the dosing regimen is weekly if it seems like, when you discontinued therapy, there's a prolonged effect.

Given the effects on the risk, maybe you can comment on why you selected a weekly dosing regimen for this particular medication.

DR. O'DEA: So the weekly dosing regimen was selected on the basis of the phase 2 trial, where we treated subjects, 100, 200, and 300 milligrams. And as mentioned, at that time, there was no safety signal on platelets nor on any other parameter, so the decision was made to go forward with 300 weekly in view of the severity of the disease and the grade of elevation of triglycerides that this population exhibit.
So that was the basis of it. Subsequently, to your point, yes, we did see those declines of platelets, which occurred in general around 3 to 6 months to 9 months of exposure with drug at the 300-milligram range. And that's why we decided at that point to make an adjustment to the dosing paradigm to ensure that patients could enjoy the benefits of treatment without having to discontinue treatment.

If I could just comment on the data, there is censoring of that data, as you can probably estimate. There are 1 or 2 patients whose samples weren't right on that date. They may have been a week earlier or a week later, but it had to be within 2 days of the assessed date.

DR. EVERETT: So given that you made a decision after the randomized trial to adjust the dosing regimen based on weight, you adjusted dose, but not necessarily interval. Correct? And have you tested either approach? Is the most effective way to minimize the risk by reducing the dose or is it by reducing the frequency and the dose or just
one or the other?

DR. O'DEA: So at the present time, our approach to dose reduction has been frequency reduction, just to make that clear. We've had a single presentation of 300 milligrams weekly. The patients did self-inject, by the way. I don't think we made that clear.

We are preparing a 150 syringe at the moment, recognizing what we found in our analyses of these data, that there is a weight-based element to the risks that the patients have. For the present time, alternate-week therapy is pharmacologically from the modeling perspective and also from the actual data that we have a reasonable and suitable approach to reducing dose. And again, to your point, these are drugs which can be given on a weekly, biweekly, monthly basis because of the long half-life.

We want to make sure that, for us, the preference is to move to more frequent, lower dose in the end.

DR. EVERETT: But just to be clear, you've
not actually tested any of those strategies in
their efficacy on triglycerides or their risk on
thrombocytopenia and other adverse events.

   DR. O'DEA: So we don't have any data at the
   present time. We are collecting that data at the
   present time.

   DR. EVERETT: I'm sorry. And then my second
question really has to do with the diagnosis of FCS
because it seems to be fundamental. If you look, I
think it's slide 82. Yes. On your risk management
program, in the top left, we have adult patient
with confirmed diagnosis of FCS. I haven't seen
any proposed diagnostic criteria and I know that
there's some discrepancy and difference. We heard
a little bit from Dr. Rader about how one might
make the diagnosis.

   Since this is fundamental to who gets the
drug and, from what I understand, given the unmet
medical need in a particular and focused population
where the risks which we've discussed might
actually be balanced by the benefits, we need to
know exactly who will be getting the drug.
So what's your proposal for the actual confirmed diagnosis of FCS?

DR. O'DEA: So the population we studied were populations characterized, number one, by hypertriglyceridemia greater than 750, number two by the presence of a major genetic marker for the disease, and number three, by the presence, if in the absence of a major genetic marker of a positive, that is, a low response to the LPL assay, so we use all of the --

DR. EVERETT: So you would propose a genetic test and an LPL functional assay in every patient.

DR. O'DEA: That's right. Yes, that was required for our trial.

DR. EVERETT: How accessible and available are those in the United States and more broadly?

DR. O'DEA: So the LPL assay is not that available. I'll ask Dr. Rader to talk more generally, though, about the genetic testing. Genetic testing, of course, we will facilitate, but it requires to ensure that patients are appropriately identified and can be treated
appropriately. Dr. Rader?

DR. RADER: Thank you. This is clearly a very important issue, obviously, the identification of the patients with FCS who are candidates for this medicine. It's important to point out that, currently, the diagnosis offices is a clinical diagnosis. These are patients who generally refer to lipid specialists who make the diagnosis based on clinical criteria, which include persistently elevated severe, severely elevated triglycerides over 750, not just one measurement, but multiple measurements.

The absence of secondary causes such as insulin resistance, diabetes, alcohol use, which by the way I think is an important distinguishing characteristic because many of the non-FCS patients, if not most of them who have severe hypertriglyceridemia and chylomicronemia have other secondary factors that contribute to that.

The third is the refractoriness to medication, to response to medication. Both fibrates and fish oils; at least part of their
mechanism requires good LPL activity. So I see lack of responsiveness to those existing medications as, if you will, almost a surrogate sign for a lack of good LPL activity.

Then certainly a history of pancreatitis or abdominal pain and certainly those who had some sort of presentation in childhood with either severe hypertriglyceridemia or pancreatitis is a very important criterion, not required, but certainly helps to mark a patient with FCS.

So that's the clinical diagnosis that we as lipidologists use to make this diagnosis. It's really only a tiny fraction of the broad number of patients who have chylomicronemia.

LPL testing is very attractive conceptually, but there is no clinically available assay right now and, frankly, it's a challenging assay. So we'd love to see that happen, but it's not available now.

Genetic testing, of course, is attractive as a geneticist. When you find the two mutations, you feel like you've really confirmed the diagnosis. I
think the problems with mandating genetic testing, although I think this is a discussion that needs to continue to be had, is, one, it's not currently being done clinically. It's not part of the clinical approach to this disease currently in the U.S.

Second, there are issues with how we would actually pay for those genetic testing. It's not standard right now for even insurance to pay for genetic testing. Hopefully that could be changed. And then third, it is important to point out that lack of finding two mutations in my view does not rule out the diagnosis.

There are other genes that are involved. Next-gen sequencing can miss certain types of things like large deletions. And so I do think the clinical diagnosis can be made even with a negative genetic test.

DR. O'DEA: So it sounds like you would not advocate using an LPL functional assay or a genetic test to identify patients who would be potentially candidates for using this medication.
DR. RADER: LPL testing is really attractive, but I can't advocate it in the absence of a robust, reliable test that could be used diagnostically. Genetic testing, I think, is appealing for clinicians who want to augment their clinical experience and diagnosis with a genetic test.

But I would hate to see patients who really do have FCS based on clinical criteria be denied this medication simply because we're unable to find a specific genetic mutation in the 5 genes that are currently being tested.

DR. O'DEA: Yes. I think there's that problem, but there's the opposite problem, too, which is that somebody who has an alternative cause for hypertriglyceridemia is exposed to a medication that may not have benefit for them, but has substantial risks.

DR. RADER: I certainly understand that concern.

DR. WILSON: Let's go on to the next. Dr. Low Wang?
DR. LOW WANG: Thank you. I have two questions. The first is what proof you have that the increased platelet monitoring works. So one of my concerns is that the thrombocytopenia seems to be idiosyncratic in certain instances.

Since the increased monitoring program was instituted, there have been at least 1, possibly 2 cases of severe thrombocytopenia that have occurred.

DR. O'DEA: So Dr. Stevenson spoke to the fact that one of the learnings from this is that an algorithm is as good as the adherence to it. And it's very important on our part to ensure that we have high adherence to the algorithm.

Part of the reason that we're building such a degree of support behind it is to make sure that everybody does adhere to it. In the instances where we've had patients not follow the algorithm, there has been human error. And obviously, human error is something that is a struggle to prevent.

So the patient support services, having multiple lines of communication, such that the lab
test for the patient is available through the central lab, it's available of course to the prescribing physician. It's available to the nurse case manager and through an app which is being developed or has been developed, is available to the patients.

So the physician will be informed by a nurse case manager that there is a result which is flagged to ensure that that's not missed. The lab will call the physician office to ensure that the physician is aware also, so we have two lines directly in to the physician office in case somebody failed to notice the lab result which came to the office.

So we're putting in place a number of these elements to triangulate around the possibility that somebody may not know. There's also a patient guide. There's patient education programs built into the program to ensure that the individual patient is fully aware of the need and for adherence and the risks of non-adherence.

DR. LOW WANG: I think that my concern is
that it could be idiosyncratic, so increased
monitoring would not necessarily make a difference.
So that's one question. My second question is for
Dr. Stevenson and this has to do with an element of
the REMS program and just the definition or the
rationale.

This is on slide 78. So in terms of
platelet monitoring, going back to that point, what
stable means and what the rationale is for that?

DR. O'DEA: So to your point about
idiosyncratic, yes, they're the cases that we have
listed and they're the cases that we discussed in
detail to ensure that the gradual decline is
predictable. It's the occasional patient who has
this idiosyncratic response, who is the focus of
all of this program.

DR. STEVENSON: Mike Stevenson, head of
global medical affairs. The question and the
definition as I understand it is what is the
definition of stability. The way that we have
defined it and why it was written that way in the
table is that we often leave to the discretion of
the physician on multiple readings to show some
consistency across those multiple readings at
levels above 100,000, which is a recognized value,
above which the risk of serious bleeding is
considerably mitigated.

DR. LOW WANG: I think, in this case,
though, the word stable is used for patients with
platelet counts that are below 75,000.

DR. STEVENSON: Correct. And the
recommendations for the dose regimen is pause and
resume every other week when platelets are above
100,000. So the implication -- and apologies if
it's not clear on this -- is that the levels will
go above 100,000 on multiple readings until you see
consistency of that level being at least 100,000 or
above.

DR. LOW WANG: Thank you.

DR. STEVENSON: Thank you.

DR. WILSON: Thank you. Dr. Shamburek?

DR. SHAMBUREK: Thank you. Diet therapy is
very key to the long-term success in the familial
chylomicronemia syndrome. And we've seen several
times the one slide where the placebo increases somewhere, 19 percent. And I have two questions, but the first is, do you have any follow-up on dietary compliance at the 6 or 12 months?

It seems to me that increase is likely, that that 6- or 8-week period of screening with diet was no longer followed and that would represent it. That would be one. My second question gets around probably the safety issue with your REMS proposed program. And I suspect we'll hear more about it.

But will that limit the prescriber to the inclusion criteria that you've suggested here? In my practice, it's often the children that are at the highest risk that may not make it to adulthood, that by the time they make it to adulthood, they have chronic pancreatitis.

So would a REMS program preclude off-label use and only define to that? And what is your likelihood of a patient with this getting a blood draw done 26 times a year for presumably lifelong therapy?

DR. O'DEA: So I count five questions there.
The first is the issue of diet. During the course of our trials, we did ensure that patients were instructed at every visit about diet. We did have recall on diet.

What we did not do is a random recall survey of the patients within the trial. Part of the reason is, of course, it's subjective and it's up to the patient to provide that information.

All of our patients are well-curated patients. I mentioned their age of diagnosis. They're 20 plus years into their disease. They're all at the leading centers in the world like Dr. Rader's center or Dr. Baum's center. And they are fully aware of the risk of deviating from the diet.

As regards to the REMS, it's our intent that the entry to the REMS, of course, is based on adherence to label, i.e. only those who meet the criteria for the product label, only those who are informed of the risks and benefits provided in the product label will be those who are treated.

As regards to younger patients, as
Dr. Stevenson said, our intent is that this is a drug for adult patients. We have not yet studied, although we have filed, a pediatric protocol to continue the development with a significant change in our dosing paradigm for pediatric patients for initiation in the very near future.

We also have a PIP, so called in Europe, for the continuation of development in that age group. And you're correct; the pediatric population are at risk. We do need to accelerate our access to the drug in that population, but at the present time, we have not reached the point where we have a submissible filed for the pediatric population.

DR. WILSON: Excuse me. Dr. Budnitz?

DR. BUDNITZ: Dan Budnitz. I have a clarifying question on slide CO-66, I think that Dr. Singleton was presenting. This is a figure of platelet count by study week. And as in the placebo group and volanesorsen group, N is 33 in each. How were dropouts indicated in this figure? As folks dropped out or discontinued from low platelets or any other reason, how are subsequent
platelet counts counted and included in these lines or are they excluded? So in other words, at the end of the study period, the N would not be 33 in this group. It would be much lower.

DR. O'DEA: So perhaps I'll take that question for Dr. Singleton. We believe that these are all available data in the population; i.e., the patients who are continuing in their milestone visits who may no longer be on drug.

So to your point, this represents a combination of the completers, the non-completers, and the dose-adjusted population.

DR. BUDNITZ: So in other words, people who continued the medication, but still get subsequent platelet counts are still considered on treatment?

DR. O'DEA: They are still considered in study.

DR. BUDNITZ: In study.

DR. O'DEA: In study, yes.

DR. WILSON: We're going to stop now and take a break. Some of the advisory committee members have questions and we'll come back to that.
We have a list of their names. So let's see. You had another reminder from me about lunch. Do you have that to pull it up? The advisory committee needs to choose their lunch and have their credit card with them to pay for lunch. And they can do that at the break and we'll direct you. And we'll be back in 15 minutes. Okay?

(Whereupon, at 10:04 a.m., a recess was taken.)

DR. WILSON: We are going to start in about a minute. We're going to get going and what's going to happen is, next, we're going to have the FDA make a presentation.

Then we're going to come back to the more than a handful of advisory committee questions to the sponsor, because if we want any additional estimates for things for this afternoon, it gives them more time rather than coming back after lunch.

So next is FDA, then sponsor clarifying questions, then FDA clarify. Okay? So I have to find the right page. An FDA presentation; is that going to be -- Dr. Roberts is already up there. I
DR. ROBERTS: Good morning, members of the committee. My name is Mary Roberts and I am the clinical reviewer for the volanesorsen application.

This is the outline of the topics we addressed in this morning's FDA presentations, which were previously discussed in Dr. Sharretts' introductory remarks.

I will begin with an overview of familial chylomicronemia syndrome and aspects of its diagnosis. Familial chylomicronemia syndrome or FCS is a rare autosomal recessive disease caused by biallelic pathogenic mutations in genes for the enzyme lipoprotein lipase or its cofactors, which are listed in the table below and are necessary for LPL function.

Pathogenic mutations result in absent or severely reduced LPL enzymatic activity, leading to inadequate processing and clearance of triglycerides, primarily from chylomicrons,
resulting in persistently elevated triglycerides.

Total loss of function mutations in the LPL gene are the most common mutations observed with FCS. Very few families have been described in the literature as having homozygous cofactor mutations. The prevalence for FCS is quoted as 1 to 2 per 1 million individuals.

The classic presentation of FCS is characterized by onset of symptoms in childhood or adolescence. However, symptoms may occur earlier, during infancy, and in some individuals symptoms may occur later such as during pregnancy.

Individuals with FCS have persistent very high levels of triglycerides, which increases their risk of pancreatitis. Pancreatitis is the most serious and potentially life-threatening consequence of this condition.

However, not all patients with experience pancreatitis despite very high triglyceride levels. More frequent events reported by patients living with FCS include episodic recurrent abdominal pain. Clinical signs include erupted xanthomas, lipemia
retinalis, a milky appearance to retinal vessels which does not typically impair vision, and hepatosplenomegaly. Other reported symptoms include fatigue, forgetfulness, and depression.

Currently, a restrictive low fat diet of less than 20 grams of fat is the mainstay of therapy and can be effective if adhered to. Triglyceride-lowering drugs such as fibrates typically do not reduce triglycerides in this population. There are currently no FDA-approved therapies for the treatment of FCS.

Given that there are serious safety concerns related to volanesorsen treatment, the ability to identify patients with FCS for whom benefit could be expected to exceed risk is a critical consideration.

The applicant, in their background materials, has stated that a specific diagnosis of FCS can be made by using the following clinical criteria. A patient with fasting triglyceride levels greater than 750 milligrams per deciliter that a refractory to standard triglyceride-lowering
therapy and at least 1 of the following; a history of pancreatitis as an adult or child, history of recurrent abdominal pain without other explainable cause, or family history of hypertriglyceridemia, and exclusion of other risk factors associated with elevated triglycerides such as poorly-treated diabetes.

According to the applicant, genetic testing is considered supplemental and not necessary to make a diagnosis.

Since more than 1 million Americans may have triglyceride levels greater than 750 milligrams per deciliter and since a family history of hypertriglyceridemia is likely quite common given the prevalence of diabetes and obesity in the United States, it seems unlikely that these criteria can make the diagnosis of FCS with specificity.

In contrast, a recent diagnostic algorithm for FCS proposed genetic testing as a fundamental step in establishing the diagnosis in patients clinically suspected of having FCS.
Furthermore, a recently updated gene review stated that the majority of individuals with chylomicronemia and plasma triglyceride concentration greater than 2,000 milligrams per deciliter do not have familial LPL deficiency, which is the most common cause of FCS.

This afternoon, the committee will be asked whether the proposed treatment indication of familial chylomicronemia syndrome without further definition specifically identifies a patient population for whom volanesorsen may have a favorable benefit-risk profile.

I will now discuss the key interactions between the division and the applicant that resulted in the volanesorsen phase 3 program. At the end of phase 2 meeting in 2014, major topics of discussion included the patient population, selection of endpoints, the adequacy of the safety database, and the appropriateness of the dose, which are summarized in this table.

Two topics discussed, clinical endpoints and dose selection, call for further attention. The
primary endpoint of triglyceride reduction in adult
patients with FCS was considered acceptable.
However, given the uncertainty regarding direct
clinical benefit to patients when using a biomarker
to support approval, the Division strongly
recommended assessing other outcomes that would be
meaningful to patients living with FCS.

In the phase 3 trial, a patient-reported
outcome measurement for abdominal pain, quality of
life questionnaires, and adjudication of
pancreatitis events were incorporated to more fully
inform the meaningfulness of triglyceride lowering.

In addition, the Division encouraged the
applicant to study more dosing regimens than only
300 milligrams per week in the phase 3 program in
case this regimen proved less safe or tolerable
than anticipated. No further phase 2 dose
exploration trials were initiated and phase 3
trials utilized a single dose regimen of 300
milligrams per week.

Following these discussions, 2 randomized
placebo-controlled studies were initiated called
study CS6 and CS16. CS6 is considered the pivotal study to support the efficacy and safety of volanesorsen in patients with FCS. CS16 provides supplemental safety data.

Due to serious events of thrombocytopenia, the dosing interval for all patients in CS16 was changed to every other week at week 13, with the exception of patients that had received 5 months or more of treatment.

CS7 is an ongoing open-label extension study in patients with FCS. Next, the key inclusion criteria will be highlighted. Patients enrolled in study CS6 qualified for participation by having a history of chylomicronemia, defined as lipemic blood or triglycerides greater than 880 milligrams per deciliter as well as a fasting triglyceride greater than 750 milligrams per deciliter at screening, documentation of a genetic profile consistent with FCS or documentation of low LPL activity, and most patients were required to have a history of pancreatitis.

Patients enrolled in CS16 required a fasting
triglyceride of greater than 500 milligrams per
deciliter in order to participate. Eligibility
criteria related to FCS for the open-label
extension study were the same as the pivotal trial.

The baseline characteristics of CS6 and CS16
are shown in this slide. Within the respective
trials, baseline characteristics were well matched
between treatment groups and are not shown.

Compared with the trial population in CS16,
the patients with FCS in CS6 were slightly younger.
There was a lower proportion of men and BMI was
lower. As expected, baseline triglyceride values
and percentage of patients with a history of
pancreatitis were higher in the CS6 population.
Study CS16 had more patients with a history of type
II diabetes and concomitant use of statins compared
to patients in study CS6.

Recurrent abdominal pain is a characteristic
symptom that adversely affects the quality of life
of patients with FCS. Starting during the 6-
to 8-week diet run-in period through the end of the
study, patients completed a weekly disease symptom
Interestingly, during the screening period, the majority of patients did not report having any abdominal pain. Furthermore, of the patients reporting pain at least once during this period, only 6 patients in CS6 reported their worst weekly maximum pain intensity as 7 or greater.

As mentioned earlier, patients enrolled in study CS6 qualified on the basis of prior documentation of an FCS-associated genotype or on the basis of prior documentation of LPL deficiency in association with other qualifying inclusion and exclusion criteria.

Testing via next-generation sequencing of hypertriglyceridemia-related genes was subsequently performed on study in the reference laboratory for patients who consented to such testing.

The applicant reported that 9 of 66 patients who had screening triglycerides of 750 milligrams per deciliter or higher did not have confirmatory on-study testing consistent with FCS.

For 3 of these patients, the initial
assessment that their genotype was consistent with FCS and qualified them for participation was not confirmed by the on-study geneticist. Six of these patients were enrolled based on low LPL activity by medical history or initial on-study LPL activity testing that was not subsequently confirmed by the reference laboratory or not done.

These examples suggest that the diagnosis of FCS may not be straightforward, since some patients who investigators believed had FCS who had triglycerides greater than 750 milligrams per deciliter and even a history of pancreatitis did not have a diagnosis confirmed with on-study testing.

How best to identify a patient population for whom volanesorsen may have a favorable benefit-risk profile should be kept in mind while considering the efficacy and safety profile of volanesorsen.

The next part of the presentation will consider the efficacy observed in volanesorsen therapy in patients with FCS. The efficacy
evaluation relies on a single trial, CS6. The primary endpoint was the change in triglycerides at month 3.

Other endpoints of interest include abdominal pain, quality of life, and pancreatitis. The strengths of this trial include use of a placebo control, the duration, the adjudication of pancreatitis events, and the attempt to capture a patient-reported outcome, abdominal pain.

Limitations of this trial include the lack of additional systematic collection of other outcomes that may be clinically meaningful to patients living with FCS and the high rate of discontinuation in the volanesorsen arm.

The statistical reviewer, Dr. Alex Cambon, will discuss these topics further.

**FDA Presentation – Alexander Cambon**

DR. CAMBON: Good morning. My name is Alex Cambon. I am the statistical reviewer of this application and will be presenting the efficacy results.

This is an outline of the topics I will
cover. I will give a brief overview of the primary and secondary endpoints for study CS6. After describe treatment discontinuation and missing fasting triglyceride data or TG, I will discuss the treatment effect for primary and secondary endpoints as well as evaluations of select exploratory and post hoc analyses.

I will then discuss issues with these exploratory and post hoc analyses, including difficulty in interpretation due to the large number of these analyses. Then I will end with a summary of the statistical issues and conclusions.

These are the primary and secondary endpoints for study CS6. Note that these were the only endpoints included in the hierarchical multiple testing procedure to control type 1 error. The primary efficacy endpoint was percent change from baseline and fasting triglycerides at 3 months.

Secondary endpoints included percent change in fasting triglycerides at 6 and 12 months, proportion of patients achieving various
triglyceride cut points, change in hepatic volume, and two outcomes incorporating abdominal pain and/or pancreatitis that are of special interest and will be discussed in detail later.

Now, I will describe the extent of treatment discontinuation and missing triglyceride data on the two treatment arms.

In this figure, the X axis represents weeks from randomization, and the Y axis the proportion of subjects were still on treatment over time. The red line with long dashes represents the volanesorsen arm and the black short dashed line is for the placebo arm.

The graph demonstrates that patients on the volanesorsen arm discontinued treatment at a much higher rate than those on the placebo arm. By 6 months, 9 of 33 or 27 percent of subjects discontinued volanesorsen while only 1 subject discontinued placebo.

By 12 months, almost half had permanently discontinued volanesorsen treatment. Note that, here, we are describing permanent treatment
discontinuation. There were more patients who had
dose changes or interruptions on volanesorsen.

Now, I will show how treatment
discontinuation impacts missing data. This table
shows the relationship between treatment
discontinuation and missing triglyceride data.
Some, but not all patients who permanently
discontinued randomized treatment were followed up
for triglyceride assessments. Only 1 volanesorsen
patient had discontinued treatment and there were
no missing data on either arm at 3 months, the time
point of the primary endpoint assessment.

However, there were increasing amounts of
missing data over time impacting the assessment of
secondary endpoints. For example, 6 subjects or
18 percent of the volanesorsen arm were missing the
12-month triglyceride assessment compared to only
1 subject or 3 percent of the placebo arm.

All 6 subjects in the volanesorsen arm with
missing 12-month triglyceride data had also
discontinued treatment. This increasing treatment
discontinuation and missing data on volanesorsen
over time helps to understand triglyceride results shown on the following slides.

Next, I present some key triglyceride results. The analysis results demonstrated superiority for the primary endpoint of percent change in fasting triglycerides at 3 months using the applicant's ANCOVA method.

On average, there was a 77 percent reduction in triglycerides at 3 months on volanesorsen as compared to an 18 percent increase on placebo. This yielded a statistically significant absolute difference in average percent change of 94 percentage points in favor of volanesorsen.

This figure compares the cumulative distribution for percent change in triglycerides at 3 months for the volanesorsen and placebo groups. The X axis represents the percent change in triglycerides. Since decreases in triglycerides are desired, better or lower values of percent change are toward the left side of the graph.

The Y axis is the corresponding proportion of patients in each group who had the degree of
percent change shown on the X axis or better.
There was a large separation between the cumulative
distribution functions for volanesorsen and placebo
groups.

For example, the vertical line at 40 percent
reduction in triglycerides shows that 88 percent of
patients on the volanesorsen arm had at least a
40 percent reduction compared to only 9 percent of
patients on the placebo arm.

At month 6, there was still a large and
significant treatment difference in percent change
in triglycerides, but the average effect in all
randomized patients was attenuated somewhat
compared to month 3. This is probably due to the
increased treatment discontinuation at month 6 on
the volanesorsen arm shown in a previous figure.

The applicant's method of imputing missing
data relies on a missing-at-random assumption and
treatment discontinuation is not taken into
account. Since missing data are strongly
associated with treatment discontinuation and any
effects of treatment are likely to go away after
treatment discontinuation, the missing-at-random assumption is probably not accurate.

For this reason, I implemented a wash-out imputation which assumes that the profile of subjects with missing data is similar to the profile of subjects on the placebo arm.

At month 12, there again was a large and significant difference, although there was further attenuation of the estimated treatment effect relative to earlier time points, again probably due to the increasing discontinuation over time on the volanesorsen arm.

Analysis of the proportion of patients with 3-month and 12-month triglyceride assessments less than select threshold values showed a similar pattern. There was again a consistently large separation between groups at 3 months for each threshold.

However, the 12-month triglyceride threshold analyses, while still all showing a statistically significant difference between treatment groups, had large attenuations in the separation compared
to 3 months.

For example, 82 percent of patients on volanesorsen had a 3-month triglyceride assessment below 1,000 milligrams per deciliter. However, at 12 months, there were only 42 percent of patients on this arm who had an assessment below this threshold value.

Now, I will present results for additional select secondary endpoints. Here again are the primary and secondary endpoints. Many of these are triglyceride-related endpoints. Given that triglyceride level is a biomarker, there was an interest in secondary endpoints that directly measure how patients function and feel.

In particular, I will now focus on the pre-specified secondary endpoints, highlighted in red, involving patient-reported abdominal pain and acute pancreatitis.

The first of these involved the average maximum intensity of patient-reported abdominal pain over the treatment period. Each week,
were asked if they had abdominal pain in the last week.

If they answered yes, they were asked to report their maximum pain intensity during the previous week on a 0 to 10 numerical rating scale as shown in the figure on the slide. To obtain the average maximum intensity for a patient, these weekly maximum intensity observations were averaged over all weeks during the treatment period.

The other planned secondary endpoint that measured how patients function and feel was a composite endpoint involving both abdominal pain and acute pancreatitis. The number of composite events, defined as either an abdominal pain score of at least 4 during the on-treatment period, or an adjudicated pancreatitis attack during the on-treatment period, was calculated for each patient.

From this, a yearly rate or frequency was derived for each patient. These frequencies were then averaged over all patients at each treatment group.

This figure shows the missing data pattern.
over time for abdominal pain, including intermediate missing data. The solid red line on top is the proportion of missing data for volanesorsen over time and the black dotted line is for the placebo arm.

As with triglycerides, there was an imbalance with a consistently higher missing data rate on the volanesorsen arm during the treatment period. Also, NOT shown, there were 7 patients on the volanesorsen arm versus 1 on the placebo arm that were not followed up for the entire 12-month period for acute pancreatitis attacks.

Analyses of abdominal pain and acute pancreatitis generally assumed missing data after dropout were missing at random, a questionable assumption given the greater dropout on volanesorsen.

Furthermore, some analyses compared treatment groups with respect to counts or proportions of patients experiencing an event. These analyses are particularly problematic and likely biased toward volanesorsen.
Given the differences between treatment arms in discontinuation, the placebo group would be expected to show a greater frequency of events simply due to the greater follow-up time, even if volanesorsen had no effect.

Here are the results of these select secondary endpoints that directly measure how patients function and feel. Since the measurements involve pain and acute pancreatitis, higher values represent worse outcomes. We can see that not only are these analyses not statistically significant, but since the treatment difference is positive for both endpoints, they also lack any favorable trend toward the study drug.

For example, the on-treatment rate of either a weekly abdominal pain score greater than 4 or an acute pancreatitis attack was roughly 2.7 events per year on volanesorsen, as compared to 2.0 on placebo.

I also note that the hierarchical testing procedure stops at the first of these two endpoints since it is the first analysis in the hierarchy.
that is not statistically significant.

Nevertheless, we also evaluated additional exploratory analyses of direct measures of how patients function and feel to explore whether there were any supportive trends toward benefit.

In particular, we focused on additional analyses of abdominal pain, pancreatitis, and patient-reported outcome measures of quality of life in the overall study population.

Here, I present results for the proportion of patients who experienced any abdominal pain during the treatment period as well as the worst rather than the average weekly maximum intensity of abdominal pain.

For these additional exploratory abdominal pain endpoints, there is again no evidence of benefit. Next, I present exploratory results for pancreatitis attacks during the treatment period.

There were three patients with an attack on placebo as compared to 1 with an attack on volanesorsen. This difference was not statistically significant. Furthermore, as noted
previously, a comparison of counts or proportions is problematic due to the greater dropout on volanesorsen, so a comparison of the yearly rates for the on-treatment period plus 28 days averaged over all patients is also shown here with a reduced difference between the treatment groups.

While the previous slides show that there was no evidence of effects of volanesorsen on abdominal pain and pancreatitis in the overall study population, it is important to point out the limitations of these secondary and exploratory analyses.

As Dr. Roberts mentioned earlier, there was somewhat limited abdominal pain reported before and during the study, with 74 percent of patients not reporting any abdominal pain during the 6-week screening period and 56 percent not reporting any abdominal pain during the treatment period.

Furthermore, there were only 4 patients with pancreatitis events during the treatment period. This study was not enriched for patients with recent abdominal pain and was likely not
statistically powered to detect effects on these outcomes.

Therefore, while the study does not provide evidence of effects on these outcomes, it also does not rule out meaningful effects. I also evaluated results for the patient-reported outcome measures of quality of life. Here, I focus on the SF-36, which includes 8 domains. I show month 3 and month 12 change from baseline analysis results for the select SF-36 domains of physical functioning, vitality, bodily pain, and physical role functioning. For each domain, higher scores represent a better health state than lower scores, and the scores were on a 0 to 100 scale.

There were no consistently favorable trends for these outcomes. Analyses of other SF-36 domains and of EQ-5D, another patient-reported outcome measure of quality of life, also did not show any consistent trends toward benefit.

Thus, in summary, planned secondary and exploratory analyses of abdominal pain, pancreatitis, and quality of life outcomes in the
overall study population did not show any evidence of benefit.

However, the applicant has emphasized some select subgroup analyses in its application briefing document and in proposed labeling. In particular, the applicant emphasized analyses in the subgroup who had abdominal pain at baseline, and in the subgroups who had at least 1, or at least 2 pancreatitis attacks in the previous 5 years.

To interpret the results from these analyses, it can be helpful to describe where these analyses fit into the prospective plan and into the range of analyses conducted by the applicant.

Here's an overview of the huge number of endpoints and analyses that were planned and/or conducted by the applicant. There were about 10 primary or secondary endpoints pre-specified in the statistical analysis plan and included in the hierarchical testing procedure.

In addition, there were over 100 exploratory/tertiary analyses pre-specified to
varying degrees in the analysis plan, but not included in the multiple testing hierarchy.

This included those exploratory analyses of abdominal pain, pancreatitis, and SF-36 in the overall population that I just presented and that did not show any evidence of drug effects. Finally, there were greater than 100 post hoc analyses, i.e., analysis that were not pre-specified even as exploratory, but that I found in the applicant's Study Report Body or report synopsis.

The large number of exploratory and post hoc analyses creates challenges for interpretation of results. When there are so many endpoints and analyses, low p values can easily occur by chance alone even if there's no treatment effect. And positive trends may reflect chance findings.

A few of these hundreds of analyses emphasized by the applicant were unplanned analyses of pancreatitis in the subgroup with a history of pancreatitis.

In particular, here I show one such post hoc
subgroup analysis emphasized by the applicant. The numbers of patients experiencing a pancreatitis attack during the treatment period are shown here for the subgroup of subjects with at least 1 prior attack during the previous 5 years, and the subgroup of subjects with at least 2 prior attacks.

The applicant has emphasized the observation of 3 patients with events on placebo versus 0 on volanesorsen and a nominal p value of 0.02 in a subgroup with 2 or more attacks in the previous 5 years.

This subgroup analysis includes only 7 subjects on the volanesorsen arm and 4 on the placebo arm. This is a very small subgroup taken from an already very small population. Also, as discussed previously, analyses involving counts do not take into account the shorter follow-up time for patients on the volanesorsen arm and therefore bias results toward the study drug.

I also note that the complimentary subgroup analysis on the bottom row, including only patients with no prior acute pancreatitis attacks,
comprising almost two-thirds of the 66 randomized subjects, showed 1 subject experiencing an acute pancreatitis attack on the volanesorsen arm and none on placebo.

Here, I summarize issues and conclusions about the post hoc subgroup analyses emphasized by the applicant. First, it is important to recall that the secondary and exploratory analyses of abdominal pain, pancreatitis, and quality of life measures in the overall study population did not provide any evidence of a treatment effect on volanesorsen.

Furthermore, the analyses emphasized by the applicant were selected from among hundreds of analyses conducted, the vast majority of which did not show such favorable trends.

Low p values are expected just by chance with such a large number of analyses. Finally, missing data likely bias results in favor of volanesorsen, particularly for comparison of counts, as in the pancreatitis analyses shown on the previous slide.
Because of these issues, the results from the subgroup analyses do not provide convincing evidence of effects on supportive endpoints of abdominal pain and pancreatitis.

Now, I'll summarize our key conclusions about the efficacy of volanesorsen. Study CS6 demonstrated a large treatment effect on fasting triglyceride level, both in terms of the mean percent change and in terms of proportions of patients meeting various threshold levels.

However, there was no evidence of benefit with respect to abdominal pain, acute pancreatitis, or quality of life measures. It should be noted that CS6 was likely not optimally designed or powered to detect differences in these endpoints and that for rare outcomes such as acute pancreatitis the number of events was likely too small to reliably evaluate if volanesorsen has an effect.

Therefore, while these analyses do not provide evidence of effects, they also do not rule out meaningful effects. Nevertheless, these
analyses lead to uncertainty about the magnitude of
effect on direct measures of how patients function
or feel.

Sources of information outside this trial
are thus needed to characterize the expected
magnitude of direct benefit for patients and to
weigh those benefits against the risks of
volanesorsen that will be discussed in upcoming FDA
presentations. This concludes my presentation. I
will return the podium to Dr. Roberts. Thank you.

**FDA Presentation - Mary Roberts**

DR. ROBERTS: The presentation on
volanesorsen safety will cover the following
topics. I will begin by discussing my approach to
the safety review and extent of patient exposure,
followed by an overview of adverse events, serious
adverse events, and discontinuations in both
placebo-controlled and open-label extension
studies.

Then I will describe the following safety
topics of interest; injection site reactions,
immunogenicity and hypersensitivity, renal and
hepatic events, and lastly the primary safety topic of thrombocytopenia and risk of bleeding.

Individual review of the 3 phase 3 trials was the main source of data to derive my conclusions regarding the risks observed with volanesorsen therapy. The primary focus of the safety review was CS6, the 1-year placebo-controlled trial in adult patients with FCS.

Supportive safety data was provided in CS16, a 26-week placebo-controlled trial in patients with high triglycerides. Since the primary purpose of CS16 was to supplement the safety profile of volanesorsen compared to placebo, my presentation describes the comparison of all volanesorsen-treated patients with placebo, recognizing that the volanesorsen group in CS16 comprises a mixture of exposure to 300 milligrams volanesorsen weekly and every other week due to a protocol amendment.

Additional safety data was provided from patients participating in the open-label extension study, CS7.

CS7 included patients with FCS who were
treated with placebo and volanesorsen in the parent studies CS6 and 16 as well as newly identified patients with FCS. Therefore, CS7 includes patients with variable durations of volanesorsen exposure.

Serious adverse events from ongoing blinded clinical trials in other patient populations were also reviewed. Relevant events from these trials will be discussed in this presentation.

This slide shows patient exposure to volanesorsen and includes cumulative exposure for patients participating in both the phase 3 parent trials and extension studies. At the time of the NDA submission, 126 patients were treated with volanesorsen in phase 3 trials. 56 were adults with FCS.

Of these 56 FCS patients, 26 patients had over 180 days' exposure, 11 had greater than 365 days of exposure, and 1 patient had greater than 720 days of exposure to volanesorsen.

At the 4-month safety update, 25 additional patients with FCS had been exposed to treatment
with volanesorsen, yielding a cumulative total of 81 patients with FCS exposed in phase 3 trials. Of these, 23 have been treated for greater than 365 days and 5 have received treatment for greater than 720 days.

This diagram illustrates the disposition of FCS patients who were randomized into the pivotal trial, CS6, through the open-label study. 33 patients were treated with either placebo or volanesorsen.

Over the 1-year study duration, 14 patients in the volanesorsen group discontinued treatment, mostly due to adverse events. Only 1 patient in the placebo group discontinued treatment. Of the 19 patients who completed the study on volanesorsen, 5 elected not to continue treatment. While the reasons for not electing to participate in the open-label trial were not systematically collected, for 4 of the patients, there were ongoing adverse events at the time of study completion, including low platelet counts.

Fourteen patients treated with volanesorsen
in CS6 elected to participate in the open-label extension study. Of these, an additional 5 patients discontinued, leaving only 9 out of the original 33 patients as of the 4-month safety update on volanesorsen.

Of the 9, only 1 remains on 300 milligrams of volanesorsen weekly. Nearly all patients in both the placebo and volanesorsen-treated groups experienced at least 1 adverse event, although there were a higher number of events reported in the volanesorsen-treated versus placebo-treated patients.

There were no deaths in the clinical program and the incidence of serious adverse events was similar or only slightly higher in the volanesorsen group compared to the placebo group. However, a substantial difference in treatment discontinuations was observed in patients treated with volanesorsen compared to patients treated with placebo.

In the pivotal trial, 42 percent of patients randomized to volanesorsen discontinued treatment
compared to 3 percent of placebo-treated patients. The most common reason for treatment discontinuation was due to adverse events.

In CS16, 20 percent of volanesorsen-treated patients withdrew due to an adverse event, mostly due to injection site reactions. There were also 2 of the 5 volanesorsen-treated patients listed as other as the reason for discontinuation, which on review of the narratives described 1 patient with a platelet count less than 50,000 and the other meeting a stopping rule for proteinuria.

The most common adverse drug reactions were events at the injection site across the phase 3 trials. Injection site reactions will be discussed later in this presentation. Excluding injection site events, the most common adverse events, defined here as occurring in at least 10 percent of volanesorsen-treated patients and greater than placebo are shown in this graph.

In adult patients with FCS, the most common adverse events were related to low platelet counts, bleeding events such as epistaxis and petechiae,
constitutional symptoms such as fatigue,
gastrointestinal events such as abdominal pain,
nausea, and vomiting, and musculoskeletal symptoms
of arthralgia and myalgia.

A similar or slightly higher proportion of
volanesorsen-treated patients reported a serious
adverse event. Important serious treatment events
included thrombocytopenia, serious events of
hypersensitivity, and events associated with flu-like reactions.

As mentioned earlier, volanesorsen-treated
patients discontinued due to adverse events and
more frequently than placebo-treated patients. In
the pivotal trial, 9 volanesorsen-treated patients
compared to no placebo-treated patients
discontinued due to an adverse event.

The most common reason for discontinuation
was related to low platelet count followed by
fatigue. Many of the events resulting in treatment
discontinuation are symptoms or signs of specific
safety concerns associated with volanesorsen
treatment which will be discussed in more detail.
These safety topics include the following, injection site reactions, immunogenicity and hypersensitivity, renal and hepatic events, and lastly thrombocytopenia and risk of bleeding. The first safety topic is injection site reactions. Adverse events at the injection site were the most common event reported in all phase 3 trials. In study CS6, no placebo patient reported an injection site reaction. And 79 percent of volanesorsen-treated patients reported almost 500 individual events.

The average number of injections in the pivotal trial before the first reported injection site reaction was 6 with a range of 1 to 34 injections. The median time to resolution of these events was 8 days. Skin discoloration was noted in 20 to 30 percent of patients at the injection site in phase 3 trials.

Five patients in CS6 and 16 patients in CS16 had discoloration events at the injection site that had not resolved. 1 patient in the pivotal trial discontinued due to an injection site reaction and
is discussed next. This patient with FCS was randomized to volanesorsen, 300 milligrams per week, and received a total of 13 doses. An adverse event at the injection site was reported on study day 1.

In total, this patient experienced 25 adverse events at the injection site. No concomitant medications were administered for these injection site reactions. The patient discontinued from volanesorsen treatment due to injection site reactions and fatigue, but continued in the study and completed follow-up in study week 52.

Hyperpigmentation, loss of sensitivity, and skin depression at the injection site were ongoing at the follow-up visit. These photos were taken approximately 4 months after the last administration of volanesorsen.

The next topic is immunogenicity and hypersensitivity. Volanesorsen antidrug antibodies were analyzed at baseline approximately every 4 to 13 weeks. Of the 33 volanesorsen-treated patients in the pivotal trial, 11 patients or 33 percent
tested positive for antidrug antibodies. The median time of onset was approximately 6 months. In general, positivity was persistent from onset through the last evaluation. Development of antidrug antibodies did not appear to affect triglyceride levels or platelet count over time for the 11 patients positive for antidrug antibodies in the pivotal trial.

Review of a serious hypersensitivity reaction of serum sickness and anaphylaxis noted a potential association with development of anti-volanesorsen antibodies, which will be discussed in a moment.

Overall, there was a higher proportion of volanesorsen-treated patients compared to placebo-treated patients reporting a hypersensitivity event in both CS6 and CS16. Within the volanesorsen treatment group, there was a slightly higher proportion of ADA-positive patients compared to ADA-negative patients reporting an event. However, the number of patients are small.

In both CS6 and 16, erythema was reported by
the largest number of patients. Although not
classified as a serious adverse event by the
applicant, a patient in CS6 developed itching and
erythema extended to whole body surface after
3 months of dosing despite the use of oral and
topical antihistamines for previous injection site
reactions.

The persistent erythema led to an ER visit,
discontinuation of volanesorsen, dermatology
consultation, treatment with steroids,
antihistamines, and eventually cyclosporin.

Two serious cases of hypersensitivity
occurred in non-FCS patients and will be discussed
next. The first case is a 47-year-old man with
hypertriglyceridemia, randomized at 300 milligrams
of volanesorsen weekly. After his 18th and
19th doses, the patient developed flu-like
symptoms.

Volanesorsen was held. 19 days after his
last dose of study drug, the patient reported fever
of 104 degrees Fahrenheit and pain coincident with
the development of high positive anti-volanesorsen
antibody titers which peaked to 25,000.

The patient was started on high-dose prednisone. A rheumatologist diagnosed this patient with serum sickness.

The second case is from an ongoing clinical trial in a different study population. This patient while on volanesorsen, 300 milligrams per week, developed vomiting, nausea, muscle aches within 12 hours of dosing, starting with his 17th dose.

Within 5 minutes of his 25th dose, the patient experienced an event described as anaphylaxis that required emergent administration of epinephrine. The patient recovered from the event and discontinued treatment.

This patient had been negative for anti-volanesorsen antibodies and then converted to positive, which were present at the time of the anaphylactic reaction.

Flu-like reactions were events of interest and defined by the applicant as either flu-like illness, or pyrexia, or feeling hot, or body
temperature increased plus at least 2 of the following symptoms, chills, myalgia or arthralgia starting on the day of injection or the day after.

Case report forms did not prospectively ask about each of these symptoms. Therefore, patient and investigator would have had to report up to 3 signs and symptoms as adverse events within a narrow time window to meet the definition for a flu-like reaction.

This approach may underestimate the number of patients with flu-like symptoms associated with volanesorsen treatment. Therefore, an analysis was conducted using a more sensitive definition of flu-like reaction defined as reporting any of the following events, starting on the day of injection or next.

The results of both analyses are shown in this table. Using a stricter definition of flu-like reaction, only 2 in each of the phase 3 studies, 2 patients in each of the phase 3 studies met the criteria.

Using the more sensitive FDA definition,
additional patients reported symptoms suggestive of
a flu-like reaction with volanesorsen
administration. The next safety topic to consider
are renal-related events.

Serious events of renal toxicity have been
associated with other antisense oligonucleotides
and, in the volanesorsen non-clinical program,
there was accumulation of drug in the kidney of
non-human primates with resulting tubular
vacuolation and proteinuria at clinical exposures.

In CS6, there were a small number of renal-
related adverse events reported, which mostly
reflected changes in laboratory values that were
transient and mild.

There was 1 case of acute kidney injury, but
it was temporally associated with acute diarrheal
illness and hypotension and it resolved with volume
resuscitation. There were 4 patients who had at
least 1 modest increase in creatinine, but which
exceeded 0.3 milligrams per deciliter or 50 percent
above baseline.

In CS16, 2 volanesorsen-treated patients met
renal-related stopping rules. 1 was for worsening proteinuria from a baseline 242 milligrams per day to approximately 1,500 milligrams per day after approximately 3 months of treatment.

Although this patient had type II diabetes and proteinuria at baseline, there was no clear explanation for such an increase over this short duration. The other patient met a stopping rule for increased creatinine, but was able to continue in the study after a temporary treatment pause.

A higher incidence of renal-related adverse events was reported in CS16, 16 percent of volanesorsen-treated patients versus 8 percent of placebo, but none were serious. In summary, there is no clear evidence for nephrotoxicity, including immune-mediated etiologies.

A significant limitation of this program was that proteinuria was not well quantified since urine creatinine was not measured. Therefore, it is possible that volanesorsen has an adverse effect on the kidney that may have gone undetected to date.
Given this limitation as well as the small safety database, continued monitoring for a potential renal adverse effect is warranted.

The next safety topic for discussion are hepatic-related events. Small numbers of patients treated with volanesorsen were noted to exceed safety thresholds for ALT and AST elevations in CS6 and CS16. 2 volanesorsen-treated patients in study CS16 met a stopping rule related to elevations in liver enzymes.

One of these patients is depicted in this slide. Her lab values over time for ALT are shown in gold and AST in purple. After receiving 4 doses of volanesorsen, the patient's ALT was 8 times the upper limit of normal and AST was 10 times the upper limit of normal. Bilirubin was within normal limits.

No alternative etiology was determined. After discontinuation of volanesorsen, liver enzymes returned to baseline. In general, elevations in liver enzymes were noted in a small group of volanesorsen-treated patients which
resolved with discontinuation of treatment.

Association with volanesorsen cannot be definitively ruled out. There were no cases of Hy's Law, an indicator of drug-induced liver injury noted with volanesorsen treatment.

The last safety topic is thrombocytopenia and the risk of bleeding. This table below describes the changes to platelet monitoring and volanesorsen dosing as the clinical safety signal of volanesorsen-induced thrombocytopenia emerged. Please note the last column refers to amendments to platelet monitoring and treatment discontinuation that occurred after the last patient in the pivotal trial had been dosed and impacted patients in the ongoing open-label study.

Over time, the frequency of platelet monitoring increased from 4 to 6 weeks to weekly. The threshold for permanent discontinuation of study drug became more stringent. The number of dose re-challenges were limited and the dose interval for volanesorsen was changed to every other week for platelet counts that fell below
This figure shows all platelet measurements over time for the placebo group in blue and the volanesorsen group in red for the pivotal trial. The average baseline level of platelets in CS6 was 228,000 and 215,000 in the placebo and volanesorsen groups respectively.

Two types of platelet reduction have been observed with volanesorsen treatment. The first is exhibited by the gradual decline noted in platelet count of approximately 30 percent on average within the first 6 months.

However, this description does not fully characterize the clinically significant platelet reductions observed with volanesorsen treatment. Individual volanesorsen-treated patients experienced a second type of platelet reduction noted for rapid, severe decreases in platelet count.

The number and percentage of patients with nadir platelet count meeting categorical thresholds at any time post-baseline are described in the
table below for patients in the phase 3 trials.

It is notable that, although the applicant has presented data, patients with FCS have significant variability in platelet count, suggesting that significant thrombocytopenia may occur as part of the natural history of the disease.

In CS6, a 52-week randomized placebo-controlled trial of patients with FCS, the incidence of thrombocytopenia was substantially higher among volanesorsen-treated patients than placebo-treated patients.

Please also note that, as of the 4-month safety update, there were 7 patients in the phase 3 trials that experienced a platelet nadir of less than 50,000, 3 of whom had platelet counts less than 25,000 for grade 4 thrombocytopenia.

This table does not include 2 additional patients with platelet counts less than 50,000. One case occurred in the phase 2 dose-finding study and another case occurred after the 4-month safety update cutoff.
Overall, there were 9 patients, 8 of whom were patients with FCS with a platelet count less than 50,000. The lowest platelet count ranged between 8,000 and 49,000. 8 of these patients are represented in this slide, as these patients had experienced the event by the 4-month safety update. The 9th patient was reported in February of this year as a 15-day safety report. This event of thrombocytopenia was reviewed as part of the volanesorsen application and is included in this discussion.

No patients had a major clinical bleeding event, although 4 had minor clinical bleeding events such as epistaxis and petechiae as represented by the red triangle. The time to onset from the start of volanesorsen to a count below 50,000 was highly variable, with a range of 51 to 300 days.

All patients recovered with discontinuation of volanesorsen and in 6 patients with administration of steroids, including 1 patients who also received IVIg. 2 patients were re-
challenged with weekly volanesorsen dosing.

Patient D was able to maintain a platelet count greater than 100,000. However, patient G had a second platelet nadir less than 50,000 when re-challenged with volanesorsen. In 3 patients, patient E, F, and the latest case that is not included on this slide, switching the frequency of volanesorsen dosing to every other week did not result in stabilization of platelet count.

Lastly, under enhanced platelet monitoring, which included biweekly monitoring of platelet count and dose adjustment, which was implemented when patient A and B experienced a platelet count less than 25,000, there have been an additional 4 patients in the ongoing open-label trial with platelet counts less than 50,000, including 2 patients with platelet nadir of 15,000 and 17,000 respectively.

One of these patients was the most recently reported case. This is a graphical profile of the 9th patient. The green line and blue dots represent platelet counts from the central and
local labs respectively. The pink line represents triglyceride levels.

The vertical lines represent either placebo or volanesorsen administration. This patient with FCS and no history of pancreatitis was randomized to placebo in CS6. She enrolled in the open-label extension study and started on volanesorsen, 300 milligrams per week.

She was switched to every-other-week dosing due to a low platelet count. The patient administered a dose of volanesorsen despite a previous low platelet count of 69,000. Her platelet count dropped to 17,000. The patient received steroid therapy and the platelet count rebounded. The patient did not report any clinical bleeding.

Despite the patient and investigator, complying with the protocol-directed platelet monitoring at a minimum weekly, a treatment pause did not occur and the patient was dosed. Grade 4 thrombocytopenia occurred approximately 300 days after starting treatment with volanesorsen.
The proposed platelet monitoring and dose adjustment may not prevent precipitous drops in platelet count. And it is unknown if this monitoring strategy will be able to quickly identify patients with very low platelet counts and intervene before a serious bleeding event occurs in a real-world setting.

Thus far, investigations into the mechanism of volanesorsen-induced thrombocytopenia are inconclusive.

In addition to platelet counts, the incidence of clinical bleeding was evaluated in the pivotal trial. In an FDA analysis of the pivotal trial, after excluding bleeding events at the injection site and terms that only related to a laboratory value, there was still a higher proportion of volanesorsen-treated patients with clinical bleeding compared to placebo with the most frequent bleeding events being epistaxis and petechiae.

This slide summarizes the clinical bleeding events by the lowest previous platelet count. It
is of concern that clinical bleeding occurred for most patients above 75,000, a value where one would not expect spontaneous bleeding, suggesting a possible effect on platelet function rather than only platelet number.

To date, an assessment of platelet function in FCS patients exposed to volanesorsen has not been conducted. The use of anticoagulant and/or antiplatelet medication in bleeding events was also evaluated.

Patients who were taking these concomitant drugs were more likely to experience bleeding in both volanesorsen and placebo groups than patients who were not taking them. An analysis for an interaction between volanesorsen and antiplatelet anticoagulants with respect to bleeding events was not significant, but the small number of events preclude definitive conclusions.

The applicant has proposed a new dosing regimen for volanesorsen based on platelet count and body weight in an attempt to reduce the risk of severe thrombocytopenia and bleeding with
volanesorsen treatment.

   Dr. Yunzhao Ren will now discuss the applicant's proposal.

**FDA Presentation - Yunzhao Ren**

   DR. REN: Good morning. My name is Yunzhao Ren, the clinical pharmacology reviewer of volanesorsen. I'll first introduce the PK characteristics of volanesorsen followed by applicant's dose selection rationale for phase 3 studies and, last, I will spend some time discussing applicant's proposed dosing regimen adjustment to mitigate the increased risk for severe thrombocytopenia.

   The absolute bioavailability of volanesorsen, 300 milligrams subcutaneous injection, is approximately 80 percent. Although the study dosing regimen is once weekly, about 95 percent of the weekly systemic exposure is concentrated on day 1.

   Volanesorsen has a maximum concentration or Cmax is reached approximately 4 hours post-dose.

   And at the end of the dosing day, volanesorsen mean
plasma concentration drops to about 5 percent of
the mean Cmax value.

Afterwards, volanesorsen plasma
concentration decreases slowly to about 1 percent
of the mean Cmax value at the end of the week.

Animal studies indicate that the initial
elimination phase of volanesorsen is mostly due to
the wide distribution through the peripheral
tissues. In the human relevant animal model,
cynomolgus monkey, the hepatic concentration is
about 60-fold higher than the plasma peak
concentration.

In a mass balance study in rat, it shows
that the drug exposure in bone marrow is
approximately 200-fold higher than the exposure in
plasma.

Next part, I will discuss applicant's dose
selection rationale of volanesorsen. Phase 2 study
CS2 was the only dose-ranging study conducted in
volanesorsen clinical program. It was a randomized
double-blind placebo-controlled parallel group
dose-ranging study in adults with severe or
uncontrolled hypertriglyceridemia.

The inclusion criteria for fasting triglyceride serum concentration at screening were at least 440 milligrams per deciliter if patients were not on triglyceride-lowering therapy or at least 225 milligrams per deciliter if patients were on a stable well-controlled dose of fibrate or patients with FCS diagnosis.

Enrolled patients were divided into 4 groups, a once weekly treatment for 13 weeks. Group 1 and 2 were on once-weekly monotherapy of placebo, of volanesorsen, 100, 200, or 300 milligram. Group 3 was a combination therapy of fibrate plus placebo or volanesorsen, 200 or 300 milligram. Group 4 was a proof of concept, open-label group of 3 patients with FCS diagnosis.

apoC-III is the target protein of volanesorsen. Dose-ranging studies demonstrate that, following 13 weeks once-weekly treatment, there is a dose-dependent and time-dependent reduction of apoC-III serum mean concentration from the baseline in patients on volanesorsen.
monotherapy.

apoC-III reduction status date appears to have reached approximately at week 13. Similarly, a dose-dependent and time-dependent reduction of triglyceride serum mean concentration from baseline was also observed in the same patient population.

Triglyceride reduction steady state appears to have been reached approximately at week 9. In addition, a dose-dependent and time-dependent reduction of mean platelet count from the baseline was observed in the same study for all 4 treatment groups.

However, the steady state of mean platelet reduction appeared to not have reached at week 13 in this study. Of note, in this study, 1 patient with FCS experienced severe thrombocytopenia with platelet count reduced to less than 50,000 per microliter on the second day after week 13 dose, which is the last dose.

At an end of phase 2 meeting, the applicant proposed a plan to carry 300-milligram once-weekly dosing regimen into phase 3 studies based on the
results from study CS2. However, FDA commented that applicant's development program to date was extremely limited and it took a substantial risk proceeding with just one dosing level into phase 3 studies.

Next part, I will discuss the assessment of applicant's proposed dosing regimen adjustment to mitigate the increased risk for severe thrombocytopenia. The discussion will start with more observations from phase 3 studies.

Consistent with study CS2, phase 3 study CS6 also demonstrated a time-dependent mild to moderate reduction of mean platelet count from baseline in patients with FCS upon 300 milligrams of volanesorsen once-weekly treatment.

In study completers, as shown in this figure, a steady state of mean platelet count was with approximately 37 percent reduction from baseline, appeared to have reached at about week 32 in the volanesorsen treatment group.

At the steady state, the absolute mean value of platelet count was approximately 130,000 to
140,000 per microliter, which is lower than the
lower limit of normal range of platelet count.

Also in the volanesorsen treatment group,
13 out of 19 study completers, two thirds of them
had at least one platelet count reduced to lower
than 100,000 per microliter during this study.

However, other than time-dependent mild to
moderate reduction of mean platelet count from
baseline, we noticed there was another type of
platelet reduction in phase 3 studies. As shown in
this slide, 7 more patients experienced severe
thrombocytopenia in phase 3 studies by cut-off data
of 4-month safety update other than the first
patient H from study CS2, who had low platelet
count at baseline.

The other 7 patients had normal platelet
count at baseline. The hallmark of the platelet
reduction pattern in these 7 patients is a rapid
precipitous decline of platelet count in short
period of time.

Some patients had platelet count dropped
from normal range to less than 50,000 in just one
month, with maximal reduction rate of about 45,000 per week. In addition, the time to onset in these patients tends to occur at an earlier time point.

One patient experienced the severe thrombocytopenia as early as on day 51 and the majority of these patients first experienced thrombocytopenia in less than 14 weeks. Therefore, it is fair to separate the platelet reduction pattern of these severe cases from the time-dependent slow platelet reduction pattern observed from the previous slides.

We tend to define the slow reduction pattern as type 1 reduction and the fast severe reduction pattern as type 2 reduction. This concept has been introduced by FDA for certain second-generation antisense oligos in a paper published last year, which is listed in this table.

When we summarized these 8 patients here, we noticed that 7 out of 8 patients are FCS patients, indicating that FCS patients upon volanesorsen treatment could be a potential risk factor of severe thrombocytopenia. On the other hand,
generally there's no gender susceptibility to the severe thrombocytopenia and the distribution of age and body weight in these 8 patients are quite wide.

With the concept of 2 types of platelet reduction introduced, next I will discuss the relationship between baseline body weight, drug exposure, and nadir platelet counts.

The common ground shared by FDA and the applicant is the apparent relationship between body weight and nadir platelet count observed from two randomized phase 3 studies by considering that many patients discontinued the studies and that nadir platelet values could be overestimated due to the short treatment period.

The relationship is quite impressive. The labeled points in this part are 4 patients who experienced type 2 severe thrombocytopenia in these two studies. And 3 out of these 4 patients are outside a 95 percent prediction interval of the linear model, indicating that this apparent body weight nadir platelet count relationship may not well predict type 2 severe thrombocytopenia cases.
On the other hand, I'm not saying that type 1 platelet reduction is not important, as under certain extreme conditions such as this circled patient I, who was a 71-year-old female with body weight of only 37 kilograms, experienced 75 percent reduction of platelet count from baseline, down to 50,000 per microliter at week 41.

This case represents a typical extreme case of type I platelet reduction and can be captured by this body weight nadir platelet relationship. In conclusion, the body weight nadir platelet relationship further implies the existence of two types of platelet reduction and type 2 thrombocytopenia could not be reliably predicted by the body weight.

The applicant proposed a dosing regimen adjustment plan for mitigation of severe thrombocytopenia events regardless of the platelet reduction types. The first criterion of this plan is based on the baseline of platelet count in which patients with baseline platelet count less than 140,000 per microliter will be excluded from
receiving volanesorsen treatment.

Second, the applicant proposed a once-weekly to biweekly dosing regimen switch in patients with lower platelet count based on the platelet monitoring results. And all the patients with body weight less than 70 kilograms were supposed to switch to the biweekly dosing regimen no later than month 3.

Third, patients should stop volanesorsen treatment when platelet count drops to below 75,000 per microliter. And they can be re-challenged by volanesorsen after their platelet count recovered.

Of note, the proposed dosing regimen adjustment was not pre-specified and well investigated in volanesorsen clinical studies. From a clinical pharmacology perspective, a dosing regimen adjustment based on intrinsic factors such as body weight should be justified by the rationale that the intrinsic factor is associated with drug systemic exposure and that drug systemic exposure is associated with adverse events.

Compared to the body weight nadir platelet
plot, the relationship between body weight and the volanesorsen clearance is weaker and shallower. Here, the results are from population PK dataset, which included 6 clinical studies.

For those of you who are not familiar with drug clearance, drug clearance is the reciprocal of drug exposure. The lower the value of drug clearance, the higher the systemic drug exposure.

Five patients experienced severe thrombocytopenia and with their clearance value available are plotted here as red points. If 70 kilograms is chosen as a cut-off of which the predicted clearance is 1.62 liter per hour, you will see those 5 patients are randomly distributed in all 4 quadrants, indicating that 70 kilograms may not be an optimal body weight cutoff.

In addition, 3 of these 5 patients have drug clearance higher than the population median value, indicating that their systemic drug exposure is lower but not higher than population median exposure. Therefore, it appears that there's no clear relationship between higher drug exposure and
type 2 severe thrombocytopenia events.

On the other hand, let's go to that extreme case of type 1 platelet reduction, patient I. The clearance of this female weighing 37 kilograms is 1.38 liter per hour. The case is well captured by this linear model, indicating body weight-based dose or dosing regimen adjustment may be helpful mitigating extreme cases of type 1 platelet reduction.

However, selection of non-optimal body weight cutoff for mitigation of extreme type 1 platelet reduction is tricky. As the body weight clearance relationship is shallow, for example, the clearance of patient I is only 22 percent lower than the population median clearance.

Of note, the estimated intrasubject variability of volanesorsen clearance is about 20 percent. This figure directly demonstrates the relationship between volanesorsen clearance and nadir platelet counts. Similarly, the relationship is weaker, indicating that there are some factors other than drug exposure that contribute to the
apparent relationship between body weight and nadir platelet counts.

Of note, 3 out of 4 patients experienced type 2 severe thrombocytopenia in 2 phase 3 studies, also appear as outliers in this plot.

In conclusion, generally, there are relationships between the baseline body weight, drug exposure, and nadir platelet counts in patients with severe hypertriglyceridemia, including patients with FCS.

These relationships may be helpful to predict and therefore be used to mitigate extreme type 1 platelet reduction cases based on the baseline body weight, though the appropriate cut-off of the body weight and the mitigation methods need to be further optimized.

On the other hand, all the results consistently demonstrate that the relationships between body weight, drug exposure, and nadir platelet counts could not reliably predict type 2 severe thrombocytopenia cases, as most of them are outliers of the predictive model.
Of note, close to 90 percent of the observed severe thrombocytopenia cases in volanesorsen clinical development program belongs to type 2, severe type 2 platelet reduction.

Next couple slides will switch the topic to the assessment of applicant's mitigation proposal, which is the weekly to biweekly dosing regimen switch. The regimen switch assessment will come from 3 different angles; the first, the effect of regimen switch in patients weighing less than 70 kilograms with normal platelet counts; second, the effect of regimen switching type 2 severe thrombocytopenia cases; and third, the re-challenge of biweekly treatment of the platelet count recovery.

Study CS16 has 3 subjects weighing less than 70 kilograms with normal platelet counts and they switched from weekly to biweekly regimen post-week 13. As shown here, platelet count from patient J continued a reduction trend after biweekly dosing regimen switch, whereas the other 2 patients' platelet count appeared stabilized post-switch.
However, none of the 3 patients demonstrated a clear rebound trend of platelet count after biweekly dosing regimen switch. And biweekly dosing regimen switch does not appear to mitigate the severe thrombocytopenia in some patients as shown in this figure again.

By cutoff date of 4-month safety update, there were 2 patients from open-label study CS7 who experienced severe thrombocytopenia after the dosing regimen switch from once weekly to biweekly. And the reason of regimen switch in these two patients was the low platelet count.

In the previous presentation, Dr. Roberts mentioned a third patient experienced severe thrombocytopenia after the biweekly dosing regimen switch and that was a recent event which is not listed in this slide.

For the re-challenge of volanesorsen treatment after recovery of platelet count, although we do not have a case's re-challenge with biweekly regimen, we do have a case re-challenge with once-weekly regimen after the platelet count.
recovered, as highlighted in this slide. Patient G experienced the second thrombocytopenia event after treatment re-challenged.

Here is the assessment of the biweekly dosing regimen mitigation proposal. For patients weighing less than 70 kilograms and with normal platelet counts, the effect dosing regimen switch from once weekly to biweekly after month 3 is inconclusive based on the limited observations from only 3 subjects.

Observed results suggest that the switch from once weekly to biweekly dosing regimen does not appear to mitigate the risk. And lastly, re-challenge of volanesorsen after platelet recovery is inconclusive. One FCS patient re-challenged with once-weekly treatment triggered the second thrombocytopenia event.

In conclusion, the relationship between body weight, drug exposure, and nadir platelet counts are generally helpful in prediction of extreme cases of type 1 thrombocytopenia and therefore may be used in mitigation of these cases.
However, the cutoff of body weight needs to be optimized. In addition, we don't know which is an optimal way to mitigate extreme cases of type 1 thrombocytopenia, I mean, by dose reduction or by dosing frequency reduction. Here, the applicant only proposed dosing frequency reduction mitigation plan.

For note, there's only 1 dosing strength available for the to-be-marketved volanesorsen drug product. For type 2 severe thrombocytopenia, the cases could not be reliably predicted by these relationships. Therefore, reduction of drug exposure may not be helpful in mitigation of the type 2 severe thrombocytopenia as proved by some cases that switch from weekly to biweekly regimen could not prevent the event.

Further, from the observed results, we note that the fact of biweekly regimen switch on platelet count is inconclusive in patients weighing less than 70 kilograms with general type 1 platelet reduction.

Treatment re-challenge by weekly regimen

A Matter of Record
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after platelet recovery is also inconclusive due to lack of data. In general, applicant's dosing regimen adjustment plan based on the baseline body weight and platelet counts for mitigating severe thrombocytopenia appears inadequate or minimal if not optimal.

FDA acknowledged that the algorithm of volanesorsen dose or dosing regimen adjustment is still in the process of optimization by the applicant, but at the current stage, an intensive platelet monitoring plan appears clinically critical.

This concludes my presentation and I introduce our next speaker, Dr. Chapman, for discussion of volanesorsen risk evaluation and mitigation strategies.

**FDA Presentation – Ingrid Chapman**

DR. CHAPMAN: Good morning. My name is Ingrid Chapman and I am a reviewer in the Division of Risk Management. I'll be discussing the risk evaluation and mitigation strategy considerations for volanesorsen.
A risk evaluation and mitigation strategy or REMS is a risk management plan that utilizes strategies beyond labeling to ensure that the benefits of a drug outweigh the risks. It is designed to achieve specific goals to mitigate risks associated with the use of the drug.

The FDA has the authority to require a REMS pre-approval or post-approval. A REMS may include any of the following elements; a medication guide or patient package insert, a communication plan, elements to assure safe use, which I will discuss in more detail on the next slide, and an implementation system.

A REMS must include a time table for submission of assessments. The following are requirements that may be included in a REMS with elements to assure safe use, prescriber training and/or certification, dispenser certification, which may include pharmacies, practitioners, or certain healthcare settings, where the product is dispensed could be limited; for example hospitals; documentation of safe use conditions prior to
dispensing, which may include laboratory testing, patient monitoring, and a patient registry.

The following must be considered if the FDA is contemplating elements to assure safe use. A product can be approved only if an element to assure safe use is put in place to mitigate the risk. It cannot be excessively burdensome on patient access to the drug considering patients with serious or life-threatening disease and patients who have difficulty accessing healthcare.

It must be similar to other products with elements to assure safe use that have similar serious risks and be designed to work with established drug distribution, procurement, and dispensing systems.

Now, I'd like to focus on the safety concerns of volanesorsen for which a REMS is being considered. As mentioned previously, the risk is potential serious bleeding due to severe thrombocytopenia. The specific concerns are that the mechanism of the thrombocytopenia is unknown.

The timing and severity of the platelet
reduction is unpredictable and the impact of volanesorsen and familial chylomicronemia syndrome on platelet function is unknown. What do we aim to accomplish with the risk mitigation for volanesorsen?

The primary objectives are to educate prescribers about the risk of potential serious bleeding due to severe thrombocytopenia and reinforce the need for patient counseling and monitoring. We also want to support the patient's desire to make informed decisions and continue to support the REMS for the safe use of volanesorsen.

After reviewing the safety data for volanesorsen, the FDA has developed the REMS goal shown here. The goal is to mitigate the potential risk of serious bleeding due to severe thrombocytopenia associated with volanesorsen by educating prescribers about the risk, counseling patients about the risk, and enrolling all patients in a REMS registry to further support long-term safety and safe use of volanesorsen.

To accomplish the proposed goal, we
recommend the following elements to assure safe use. I'll explain these in greater detail based on the safety considerations and requirements for each of the REMS participants.

First, I'll discuss the prescriber requirements. Prescribers must complete prescriber training and subsequently enroll in the REMS program. Prescribers must enroll patients in the REMS program using the patient-prescriber agreement form.

Prescribers also have to complete and submit a patient status form every 90 days to the REMS program. The patient status form is documentation of patient monitoring and may collect information about serious bleeds, significant declines in platelet count, and treatment modification.

Regarding pharmacy requirements to dispense volanesorsen, pharmacies must designate an authorized representative and enroll in the REMS program. The pharmacy must also verify prior to dispensing that both the prescriber and patient are enrolled in the REMS program.
Lastly, regarding patients' requirements, prior to receiving volanesorsen, patients must receive counseling from the prescriber, using the patient prescriber agreement form and enroll in a REMS program and REMS registry.

In summary, the FDA is proposing prescriber certification and training, pharmacy or dispenser certification, documentation of safe use conditions via patient-prescriber agreement form at the time of treatment initiation, routine patient monitoring that is documented every 90 days using a patient status form and enrollment of all patients in a REMS registry.

Regarding the applicant-proposed REMS, initially a communication plan-only plan REMS was submitted. We had discussions with the applicant regarding their proposal and they subsequently submitted a REMS amendment on April 4th, 2018. The applicant-proposed REMS now aligns with the FDA-proposed REMS with the same elements to assure safe use.

As the applicant presented earlier, they are
proposing additional activities beyond the REMS, which includes a patient support program. While the patient support program includes such activities as nurse case managers providing patient education and facilitating scheduling of laboratory services, it is imperative to know that these activities are voluntary on behalf of the applicant.

Because these activities are outside of the REMS, the FDA will not be able to enforce or assess these activities. Additionally, because the patient support program is voluntary, it may be discontinued at any time without notifying the FDA. In assessing the benefit-risk profile of volanesorsen, please consider that the benefits must outweigh the risks and must be sustained without the applicant's proposed voluntary activities.

We have attempted to strike a balance between safety and burden, knowing that patients should be monitored routinely. Our proposed REMS can ensure prescribers are educated and patients
are aware of the risk and the need for frequent
monitoring.

However, there are limitations to the
proposal, one being that rapid and severe decreases
in platelets may not be prevented even with
compliance with rigorous monitoring and dose
modifications per the prescribing information.

The second limitation is that the proposed
REMS will not enforce monitoring as described in
the prescribing information. It's uncertain if the
burden associated with additional requirements
would add a greater degree of safety. We'd like to
hear the committee's thoughts on the proposed REMS.
This concludes my presentation. My colleague,
Dr. Roberts, will now return to wrap up the FDA
presentation.

**FDA Presentation - Mary Roberts**

DR. ROBERTS: I would now like to summarize
our conclusions regarding the benefits and risks of
volanesorsen, which are drawn from our
interpretation of the supporting evidence and
uncertainties of the data provided and are also
considered with the underlying condition familial chylomicronemia syndrome in mind.

FCS is a rare autosomal recessive genetic condition which affects 1 to 2 people per 1 million individuals. Patients living with FCS are at risk for pancreatitis, which is the most serious consequence of this disease.

Patients with FCS also report other more frequent symptoms which may be severe and debilitating. Given that other forms of hypertriglyceridemia may mimic some of the clinical characteristics of FCS, an accurate and timely diagnosis of FCS may be challenging.

Diet is currently the primary treatment option for patients with FCS to manage elevated triglycerides, but the restrictive nature of the diet, while potentially effective is very difficult to adhere to.

Safe and effective therapies are needed to treat patients living with FCS. Following review of the data provided, a significant reduction in triglycerides was observed in patients with FCS
treated with volanesorsen. This is compelling given the typical history of ineffective triglyceride reduction with other triglyceride-lowering medications.

However, when efficacy is established by its effect on a surrogate endpoint, the magnitude of direct clinical benefit typically remains uncertain. Therefore, the benefit-risk assessment must balance an uncertain direct clinical benefit against the known and potential risks of the drug.

The risks associated with volanesorsen include volanesorsen-induced thrombocytopenia of unknown etiology which has the potential for serious bleeding. Based on the information provided we are unable to predict which patients or when they will experience precipitous platelet reductions.

Serious hypersensitivity events in patients without FCS have occurred and there is a potential connection between the emergence of anti-volanesorsen drug antibodies and these events.

Injection site reactions occur in the
majority of patients. Skin discoloration at the injection site may persist in some patients treated with volanesorsen. Imbalances in flu-like reactions and renal and hepatic biomarkers were noted. No serious events of nephrotoxicity or hepatotoxicity were observed. However, continued monitoring is warranted.

There is also concern that the benefits and risks of volanesorsen and feasibility of platelet monitoring in children has not been studied. Going forward, this will need to be addressed, given the typical onset of symptoms in patients with FCS.

Lastly, the applicant has proposed an approach for volanesorsen dosing and platelet monitoring to address the potential risk of serious bleeding with volanesorsen-induced thrombocytopenia.

The applicant has proposed that the product should be approved with a novel dosing regimen based on body weight along with biweekly platelet monitoring. This approach to dosing has not been prospectively evaluated and it is not yet clear
that it would substantially improve the safety profile for use of volanesorsen in this patient population.

The proposed platelet monitoring recommends every-two-week monitoring at a minimum for a lifelong therapy, yet when enhanced platelet monitoring was implemented in a clinical trial setting with structured oversight, strict monitoring, and dosing rules, 2 individuals experienced severe thrombocytopenia with platelet nadirs less than 25,000, including 1 who has been monitored with weekly platelet counts.

Discussion of risk evaluation and mitigation strategy options for this product have occurred in parallel with the clinical review. It is unclear whether the proposed strategies discussed thus far would be effective in preventing serious bleeding events in a post-market setting.

It is possible that a REMS may not be sufficient to ensure safe use of volanesorsen considering the data that are available at this time.
Clarifying Questions to FDA

DR. WILSON: So that's the conclusion of the FDA presentation. Now, we have two things in the near future. One is to try to address some of the issues that the sponsor may be able to work on over lunch if we have any additional data requests, things that we haven't seen up to now.

Then we have a longer list that we're not going to get to before lunch and we'll come back to. So first, for those in the advisory committee, we're going to try to make very short things. You say I want to see this after lunch, so any requests along those lines?

Yes, please state your name and what you --

DR. KANE: Robert Kane. And one of my requests is to understand a little better the magnitude of the effect on triglycerides of weekly dosing versus every other week dosing. I did see that in CS16, I believe, where there was a switch.

DR. WILSON: So that's number one weekly versus other interval dosing. Dr. Ortel?

DR. ORTEL: I would like to see better
characterization of the thrombocytopenia. I'd like to know if other cell lines are effective at the same time. I'd like to know if there are fragmented red cells or anything to suggest microangiopathic hemolytic anemia. I'd also like to know if all of the patients who dropped severely were treated with prednisone or IVIg.

I'd consider that actually a risk that these people are getting treated when we really don't know what is happening.

DR. WILSON: I think that was the second one. Any others? I had one and it's referent to sponsor slide CO-58. If in fact there was an outcome trial that was undertaken to prevent pancreatitis, what would be the number of subjects and how long might it take for persons or person years to demonstrate that volanesorsen prevents pancreatitis? And I would think that might be available. Any others? Yes? Dr. Cuaresma?

MS. CUARESMA: Definitely not a doctor. I am just a patient representative. I wish I was at this point because my question is just a little bit
more general and I think it's because maybe I don't understand.

But in the FDA, they went over; Dr. Ren had went over a single dose lasting 300 milligrams, the injection lasting 24 hours, which tells me that the half-life of that dose doesn't last long.

So how does this affect the breakdown of the chylomicrons until the next weekly dose? I guess I don't understand or maybe somebody could articulate that to me.

DR. WILSON: So as I understand it, you'd like to know more about the effectiveness again of a weekly dose versus a different interval than what the effect is on chylomicrons in the plasma over after that individual administration of a dose. Is that the question?

MS. CUARESMA: Correct.

DR. WILSON: I think that relates to the other questions about efficacy of weekly versus other dosing versus -- and we've heard this earlier for others as the dose versus interval changes. Yes, one last one, perhaps? Dr. Kane, go ahead.
DR. KANE: Just to clarify, I think I understood overall that epistaxis, bruising and bleeding, was not useful as an antecedent indication that the platelets were heading south. And that typically occurred more at a higher platelet level, 75,000 or so.

So I just wanted to understand there's no useful clinical antecedent sign or symptom that the platelets were going to go to the severe levels. Thank you.

DR. WILSON: So Dr. Kane is summarizing what many of us have said. Is antecedents prior to epistaxis or prior to bleeding or prior to more severe thrombocytopenia? We had elements of that, but predicting it of course would be of a high interest.

Then finally, Dr. Neaton, do you have another?

DR. NEATON: A quick question; you enriched the population for people with a history of pancreatitis. Did you think about, in the design of the study, given that enrichment strategy, what
fraction of people in the placebo group would develop pancreatitis during follow-up?

DR. WILSON: From the sponsor, do you need any clarifications for each of these questions that we raised? And perhaps during the afternoon session, after the open public hearing, you could make an effort to respond to these queries.

DR. O'DEA: No clarification required.

Thank you.

DR. WILSON: So now we are going to adjourn for lunch. And Latoya, what time should we be back?

DR. BONNER: 1:06.

DR. WILSON: Shortly after 1:05. Thank you.

(Whereupon, at 12:07 p.m., a lunch recess was taken.)
AFTERNOON SESSION

(1:05 p.m.)

Open Public Hearing

DR. WILSON: We're going to start in a minute or so. Good afternoon. Welcome to the open public hearing part of this program and the advisory committee reviews and recommendations, et cetera. And there's a preamble to this, so bear with me. I'm going to read this. It's a couple of paragraphs just so you understand what the open public hearing is.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency of the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you
may have with the sponsor, its product, and if
known, its direct competitors.

    For example, this financial information may
include the sponsor's payment of your travel,
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    If you choose not to address this issue of
financial relationships at the beginning of your
statement, it will not preclude you from speaking.
And for the speakers, the FDA and this committee
place great emphasis in the open public hearing
process. The insights and comments provided by you
can help the agency and this committee in their
consideration of the issues before them.

    That said, in many instances and for many
topics, there will be a variety of opinions. One
of our goals today is for this open public hearing
to be conducted in a fair and open way, where every
participant is listened to carefully, and treated
with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chair. In advance, we thank you for your cooperation.

We have several speakers. I believe we have 13 on our list. Each one will generally have a limit of 4 minutes and there will be a light system. We will encourage them to wrap up if their light comes on and they're going to go over time, so we're ready to start.

Speaker number 1, please step to the podium and, for each of you, introduce yourself, state your name and any organization you are responding for the record. Thank you. Go ahead.

MS. McCoy: Thank you. Good afternoon. My name is Nicole McCoy and I live in North Carolina. And I am very much willingly here on my own accord. And I wanted to thank you from the get-go for the opportunity to speak to you today about how I've lived with FCS for the past 16 years.

I am one in a million, so this is your lucky day. You get to meet me. But I have had FCS for 16 years, although undiagnosed for the first 10 and
it began when I got pregnant with my daughter.

I typically have an average triglyceride level between 8 and 12, 13,000. And that's common for me and that's been sustained for years. I've also had 35 bouts of pancreatitis. And at this point, I'm not willing to have another one. And that's what I really want you to understand, that I have lived with this disease and the extraordinary burdens that it has, not just physically, the pain is extraordinary, especially when you're having an attack of pancreatitis.

But there are many other burdens. There are financial burdens, social burdens, emotional, the thought of, will today be another day where I go to the hospital or will this 36th bout of pancreatitis be my last one. It's very difficult to live under those consequences every day, not just for me, for my children, my husband, my family, my friends. It really affects all of us.

I want you to truly understand that burden. As a matter of fact, sometimes I think physically I have the easy part because I lay in a hospital bed
and I just, you know, heal. It's my family who has
to endure every other challenge as I lay there
healing.

But I wanted you to think about a couple of
things that I've been through and kind of imagine
yourself in that position. My longest hospital
stay was 27 days, so I want you to imagine 27 days
without food or water. Your only nutritional
support is saline, pain medicine, potassium, iron,
magnesium, calcium, blood, transfusions,
antibiotics because of the infection on my
pancreas, and also the most difficult part of those
27 days was not seeing my children because there
was a ban in the hospital. Because of a flu
outbreak, they weren't allowed to see me.

To me, that's pretty devastating. To them,
it's devastating. And it has been just an enormous
challenge to deal with. There's a financial
burden. My family has struggled immensely. I was
a special education teacher and I had to resign two
years ago because of my illness. I was in the
hospital every 2 to 3 months.
Where I was a teacher in North Carolina, you only get 10 sick days a school year. Well, every other day, that one year, the last year I was in the hospital 4 times. I had to pay a daily rate of $250 for every day over my 10 days of sick time.

That's a huge burden. My family has lost our home. We've gone bankrupt and I'm not proud of that. But when you have $120,000 in medical bills, even though I have insurance and I thought it was really good insurance and I'm very grateful for it, there's still a huge financial burden of 35 hospital visits for pancreatitis.

So my understanding of effective people is to begin with the end in mind; seven habits of highly effective people. And the end that I want you to keep in mind is that I need your approval to move forward with this medication.

The risks that you have discussed today are far less than what I have gone through and will go through even to the point of potentially death. I'm not willing to do that. I am willing to take those risks to embrace what may come with that
medication in the hopes that I may never have to go into the hospital again,, not see my children, maybe reduce the burden financially, reduce the emotional anxiety that I do live with on a daily basis, and I just appreciate your time and what you are doing to help make the right decision. Thank you so much.

DR. WILSON: Thank you. Thank you. I remind the speakers, when the yellow light comes on, on the podium, please try to start wrapping up your presentation to stay on time and for all the speakers to get their chance.

So speaker number 2, please come to the podium, introduce yourself, and any organization you represent.

MS. HARMON: Good afternoon. My name is Mary Harmon from Hickory, North Carolina. I am here today on my own to represent myself and all those that suffer with a terrible disease, familial chylomicronemia syndrome or FCS.

I have had a terrible struggle with this disease since I was a teenager. I've had over 30
episodes of acute and chronic pancreatitis, 3
resulting in near-death experiences, in a coma, on
life support, filing for bankruptcy due to all the
medical bills, not being able to have children,
which resulted in divorce, and finally losing my
corporate job.

After being diagnosed genetically three and
a half years ago, I finally knew why I had been so
sick for most of my life. My triglycerides were
ranging from 5 to 10,000, constant pain in my left
side, xanthomas all over my body and in my eyes,
also severe brain fog and extreme fatigue.

Every day, I wondered if it would be my
last. I had never knew when an attack would occur
and was never able to make plans. Each day, I was
scared I would have to go to the ER and be treated
like a drug seeker or an alcoholic, treated like in
some way I had caused my own pain and suffering.

Once, I was cussed out by a nurse in the ER
after being diagnosed with acute pancreatitis. I
was screaming in pain and violently vomiting. The
next day, I was in a coma on life support. I had
to be shocked back to life in my hospital bed.

I was the first person in the world to go on the study drug volanesorsen. Sure, there were side effects from the drug, but having drug far outweighs the pain and suffering of the acute pancreatitis and near death experiences.

I wish I had been asked about those things that matter to the FCS patient while I was in the study. I had no hospitalizations while being on volanesorsen for three years. I was the first person in the world to finish the trial in three years and came off drug in December 2017 as required in the study. Waiting on the drug to be approved for me to take again was a hard, long waiting, nightmare.

On April 8th, a month ago, I was admitted into ICU with acute pancreatitis for eight long nights of suffering. This was the first time in three years that I'd been hospitalized. Why? Because I didn't have the drug.

Volanesorsen is my key for not getting pancreatitis and having my life back. Volanesorsen
has saved my life into treatment where nothing else is available. My triglyceride levels were down to 200, not the range of 5 to 10,000 prior to going on drug.

Please, with a heartfelt plea, as someone who actually died in the hospital and was brought back to life, I need this medicine or otherwise I will continue each day not knowing if I will be alive tomorrow.

If I were your sister, brother, or mother, father, or child, what would you do? Thank you for your time and listening to my story.

DR. WILSON: Thank you very much. Next up, speak number 3, introduce yourself and any organization you represent.

MR. SAREMI: Thank you, Mr. Chair, ladies and gentlemen, good afternoon. My name is Fred Saremi and I'm here on my own to tell my story. I was diagnosed with high lipid levels at age 30 and it gradually increased to a level of about 2,600. At times, it was as high as 8,000.

This resulted in frequent pancreatitis
episodes and trips to emergency rooms. I was referred to many specialists and none of them knew the cause or remedy for this disease. At this point, pancreatitis episodes are recurring about once every two weeks.

I'm sure you know that pancreatitis is one of the most painful experiences a person can have. The pain is comparable to a severe episode associated in passing a kidney stone. It is debilitating and disabling. I felt desperate, alone, and hopeless.

As an FCS patient, I have lived with a very unpredictable disease when pancreatitis could strike at any time, even when I followed a very restrictive low fat diet. I also had to cope with frequent and severe vomiting and diarrhea on a regular basis.

I recall many times laying on the bathroom floor for many hours so that I could be close to the toilet. In addition, I lived with the feeling of perpetual fatigue, low energy level, and a sense of mental fog.
All of these factors, a lot of anxiety, fear, and a sense of isolation due to a highly limited chance for social; this limited my social interactions quite a bit; in addition frequent absences because of pancreatitis. And it had a very negative impact on my performance.

All of these elements had a profound impact on my quality of life also. I was fortunate to participate in the third phase of the new drug, volanesorsen, and it worked great. During that time, I didn't experience any episodes of pancreatitis, vomiting, or diarrhea during the course of the trial.

I still maintain a low-fat diet. I felt great, like I never felt before. I had much more energy, no more sense of fatigue, and no more mental fog. I felt like there was a light at the end of the tunnel. I could live like a more normal life, like I used to. I wish I had been asked these kind of questions in the quality of life improvements in the questionnaires that have been asked of me.
I feel the need for regular platelet testing is a very small price to pay for all the great benefits that this drug provides. Since I have stopped taking this drug, my triglyceride levels have been gradually climbing. I have experienced some abdominal pain, but the big difference between now and the past is that I can psychologically handle it a lot better because I feel there is hope and salvation coming.

It is like I hear the proverbial bugle of the cavalry which is coming. It's coming around the corner and it's going to save me. This drug will provide hope and salvation to many of the FCS patients I personally know.

I pray and highly urge FDA to approve this drug because I believe that definitely this is a life-changing medication. I appreciate your time. Thank you and God bless.

DR. WILSON: Thank you very much. Next, perhaps speaker number 4, please introduce yourself and any organization you represent or that is supporting you.
DR. CROSS: Hello, my name is Russ Cross and I'm here on my own today to share my personal experience with the rare disease, FCS. I'm a pharmacist working as a pharmacy manager in Oregon. When I was in my 20s, I was at a trade show. One of the vendors asked me to volunteer to give some blood to test out a new diabetes machine.

It came back with a reading of over 400. I personally thought the machine was wrong. But I went ahead and went to my doctor to see what was going on. They drew my blood and had separated it into a white layer and a red layer. My triglyceride readings were over 2,500. My doctor said basically they were unreadable.

The doctor diagnosed me with diabetes, but he had no idea what to do with triglycerides other than diet and exercise. Knowledge is everything and to control my triglycerides was just something I couldn't figure out.

My father had recently passed away from pancreatitis due to high triglycerides and, because of this, the symptoms of FCS have held me back from...
pursuing many of my job goals, knowing that I may 
not be healthy enough to maintain certain job 
positions and titles.

After I turned 50, things got worse. One 
day, I had to drive myself to the ER with severe 
stomach pains. They drew my blood and, of course, 
it separated into a white layer and a red layer 
before it got to the lab. And it wasn't long 
before I got the question, are you an alcoholic.

It doesn't take long or it doesn't take much 
to make me mad, but that question does. I don't 
drink and, when you don't drink, that question gets 
old really fast. Eventually, they came back with a 
diagnosis of pancreatitis. And my one and only 
experience with this was with my father, so I just 
figured I was dying.

Honestly, I didn't realize you could even 
survive pancreatitis. I spent about a week in the 
hospital before being released. After that, my 
family doctor sent me to a lipid specialist who was 
the first and only doctor to give my condition a 
name.
After reviewing my situation, he diagnosed me with familial chylomicronemia syndrome, which even for a pharmacist is hard to say. I suffered from pain, fatigue, memory loss, diabetes, depression, fatty liver, kidney failure, and anxiety. I believe these can all be tied to my FCS condition.

Daily, I try to control my fat take. I rarely if ever drink. There is a daily fight to be good and reduce my fat content. Even doing that does not ensure me a day away from my problems with FCS.

For a long time, I've suffered with FCS alone until my specialist asked me to attend a patient advisory meeting for FCS in Portland, Oregon. There, I met three other people with FCS and this is where I really started to connect the dots. It was nice to meet people with the same condition so I could see why all this was happening, like why I have brain fog and feel run down and tired.

So much of my life, I've lived with symptoms
and conditions that doctors could not determine a cause for. The most disturbing is the number of ER visits due to stomach pain. Sharing my story with other people who understand what I've gone through helped me feel less anxious and less alone in a way I haven't felt in years.

It was a game changer for both me and my wife. So when I was given the opportunity to share my story. I wanted to be the source of hope for other people. I hope to inspire other people with FCS not to give up and to keep seeking an effective treatment and a better way of life.

I hope to help educate physicians and healthcare communities so that they can be more efficient at diagnosing FCS and I advocate for the development of new and effective treatments that will help us cope with this rare disease.

If my experience can help you gain a better understand of what it's like to live with FCS, then I feel like I've done something positive for myself and others. Thank you.

DR. WILSON: Thank you very much. Next,
we'll have speaker number 5 please introduce
yourself and any organization that is helping to
sponsor you.

MS. SAREMI: Good afternoon. My name is
Lynne Saremi. And I'm here on my own behalf today
to speak to you from a caregiver's perspective.

I've been married for over 40 years to my
husband, who you met earlier, who was diagnosed
with FCS at the age of 30. In the early years
after his diagnosis, we made lifestyle changes such
as eating a low-fat diet, beginning a more vigorous
exercise program, and those changes kept his
triglycerides at a more manageable level for many
years.

Then he required medications. And then even
with medications, diet, and lifestyle changes, his
triglycerides continued to climb.

FCS puts an extra burden on the caregiver
and the family. I live with a daily fear that my
husband will have another episode of pancreatitis.
Our family meals revolve around what he can and
cannot eat. And social events and food pose an
area of stress for both of us.

More times than I can count, my husband has
come home from an evening out and ended up with an
episode of pancreatitis. No one wants to see their
spouse sick, so it's just easier to stay home.
That creates a sense of isolation for both of us.

As a critical care registered nurse, being a
witness to my husband in chronic pain and not
knowing how to help him has been a great source of
heartache for me. To see him go through those
repeated episodes of debilitating, excruciating
pain has created a sense of helplessness and
hopelessness in me. The fear of losing him is
there every day.

The effects of this disease has caused my
husband to need a lot of downtime. FCS is also
known to cause memory loss and an inability to
concentrate. These symptoms have had an impact on
his career. He has shown up late to work because
he couldn't leave home due to vomiting and
diarrhea. He's been hospitalized many times with
pancreatitis, thus missing work.
I've changed my work schedule as a registered nurse to be home with him because I feared to leave him alone. That left me with guilt and fear when I did have to go to work.

My husband has been participating in a clinical drug trial for the drug volanesorsen over the last two years. Prior to his participation in the clinical trial, he experienced fatigue on a daily basis. He had frequent bouts of vomiting and diarrhea many times a week. He experienced severe abdominal pain several times a month.

Since the trial, my husband has had more energy, no pain, no pancreatitis, no vomiting and diarrhea. He's been a more active participant in our family activities. He's no longer sitting on the sidelines watching life go by.

He's happy and engaged and, because of that, I am happy and hopeful for our future together. This medication can be a source of hope and healing for the individuals and their families suffering from FCS.

Taking volanesorsen does require regular
monitoring, but the debilitating effects of this
disease occur on a daily basis. The regulations
for monitoring are on a regular basis. The
benefits would be felt on a daily basis. I think
daily benefit, regular monitoring says it all.

Thank you for your time today.

DR. WILSON: Thank you very much. Next
speaker is maybe two people. Speaker number 6,
please introduce yourself and any organizations you
represent.

MR. CHILDERS: My name is Mark Childers from
Palos Hills, Illinois, near Chicago. I was
diagnosed with FCS in 2016 by Dr. Michael Davidson
after having the genetic testing.

I'd been having symptoms since I was 40. My
first hospital stay was 8 days with a triglyceride
level of 14,000. What I want you guys to
understand is, before I had FCS, I had a normal
life. I took my kids out, we enjoyed life, we had
cations, I coached travel baseball.

Through this journey, I've been hospitalized
over 100 times with pancreatitis. I was told I was
fat, so I lost 70 pounds. The episodes increased.

We followed an extreme low-fat diet and then my wife, who is my savior, really, put us, as I also developed diabetes -- so we were on a low-carb, low-fat diet together.

It got worse. Took all the statins. Nothing works. Concentrated insulin, nothing works. So my new life now consists of one good day out of the week would be me being able to get up and do laundry. I have chronic pain every day.

They ask you on a scale of 1 to 10. I'm at a 5 every day. We can't take family vacations. I have to have my doctors' team notes in case I get sick here in Maryland and I have to go to the hospital.

I woke up this morning and didn't even know if I was going to be able to make it. It affects your mind. It's not just a financial thing. It's not just a physical thing. I've went to my wife and said, "I'll completely understand if you divorce me because you did not sign on for this."

My children -- who wants to have their child
come to you 10 times a day, "Dad, are you okay, do we need to take you to the hospital?"

I found out that there's a drug that can help me. And that's why I'm here today, because this is my last chance. I was told by my medical team -- I have a medical team of a lipidologist, endocrinologist, a GI -- and my GI doctor told me, "We need to be taking your pancreas out now."

I said, "Can we just hold on a little bit longer?" because I have spoken to people who have been on the drug and, even though I have five genetic mutations, I did not meet the criteria for the trial. This is my last chance. I hope you guys give it to me. Thank you.

DR. WILSON: Thank you very much. So our next speaker is speaker number 7. Please introduce yourself and any organization that's sponsoring you.

MS. GOETZ: Sorry. Good afternoon. My name is Melissa Goetz and I'm here today on my own to speak about my experience with familial chylomicronemia syndrome on behalf of the FCS
Five years ago, my 7-week-old daughter, Giuliana, was genetically diagnosed with lipoprotein lipase deficiency. After an episode of acute pancreatitis, her triglycerides were over 24,000.

At that time, I was certain of two things. One, I would never meet another individual with this one-in-a-million disease. And two, I would never in my lifetime or hers see an opportunity for treatment.

Thankfully, I am now wrong on both counts. Five years have passed and not only have I met others with FCS, but I am the cofounder and co-president of the FCS Foundation.

This position has allowed me to connect with patients and learn the real day-to-day struggles FCS has on them. The burden of disease extends far beyond diet. Members of the FCS community regularly report experiencing diarrhea, constant abdominal pain, fatigue, social isolation, memory loss, and of course the constant threat and reality
of pancreatitis, a result of high triglycerides consistently above 800 and often reaching well over 10,000.

Individuals I have met with follow low-fat, low-carb diets. They stay hydrated. They stay active. They don't smoke. They don't drink. They've met with specialists in endocrinology, metabolism, lipidology, gastroenterology. They've been on fibrates, omega 3s, and assorted cocktails of other drugs in the hopes of managing and reducing not just their triglycerides, but the day-to-day pain they experience associated with FCS with no success.

They have had unnecessary surgeries, removing their spleen, gall bladder. They have regular plasmapheresis and some have even been advised of having local surgery. They have lost their jobs, their homes, relationships. They have given up on dreams of having children of their own.

They've dropped out of school or taken less ideal jobs earning less than they would in order to accommodate their health struggles.
As with any therapy, there are sure to be side effects, PROs and cons, that must be considered. A drug that can lower triglycerides and offer day-to-day relief would outweigh the negatives, especially when no other option exists. A life without any option, the life that currently exists for FCS patients, is not a life I want for my daughter or anyone living with this disease.

I tell my three children they can grow up to be, go, or do anything they want in this life. But when I tell this to Giuliana [ph], the fear and anxiety of the realities of FCS make me wonder if I'm telling her the truth.

I thought about what a therapy for FCS would mean for my daughter when she grows up and I ask those in the FCS community what it would mean to them. And here are some of their answers in their own words, words that reflect our FCS patient survey that was included in the foundation's submission to the docket you received.

In their words, a treatment for FCS would mean not living in fear anymore that every time my
husband starts having belly pain it is going to
turn into pancreatitis and he is not going to die
an early death.

It means that my teenage grandchildren can
live a more normal life, not living with constant
pain, not living in fear of pancreatitis.

It would mean that I would be a better mom
to my daughter. The daily pain, fatigue, constant
anxiety, and dietary restrictions play a big role
in my life and trying to push through it all so
that I can be the best mom for my daughter is my
greatest challenge.

It would mean that I could breathe. I could
finally release the internal breath I have been
holding for 20 years. It would mean that I could
get a good night's sleep. My son is now two years
old. However, he was hospitalized at 3 weeks old
with life-threatening organ failure.

I wake up every couple of hours to check on
him. I want some rest for my mind and my body.

Having a treatment would ease the anxiety and
burden of never knowing if today is the day I don't
leave the hospital.

I hope my story here today helps you to understand the unmet need and burden of disease of FCS and why volanesorsen is the crucial next step in helping individuals living with FCS move forward in their lives. Thank you.

DR. WILSON: Thank you very much. Next is speaker number 8. Please introduce yourself and any organization that's sponsoring you.

DR. DAVIDSON: Good afternoon. My name is David Davidson. I'm here on my own today. As far as COI, I was a site investigator for CS7 and did attend one ad board.

Thank you for allowing me the time to speak on behalf of my patients and others who deal with this difficult condition, FCS. My name is David Davidson. I am a lipidologist in the Chicago area and I'm here on my own today to try to advocate for volanesorsen to be an option to treat this previously untreatable condition.

I know that you have and will be hearing from several individual patients, stories, and
scientific data. I would like to add the perspective of what it is like trying to care for these patients and what it is like using volanesorsen through my experience as a site investigator.

Prior to this, I had 1 patient with FCS. He had frequent episodes of pancreatitis, did not respond to any therapy I gave him, and despite his best efforts, the closest that diet could get to controlling his triglycerides was to bring his numbers down from greater than 4,425, which is the upper limit that our lab will report, to just about 6 weeks ago, he was 1,790, still at very high risk for another episode of pancreatitis.

His last hospitalization was less than 6 months ago and, clearly with his triglycerides still hovering around 2,000, it's only a matter of time before his next episode. The major problem for him is that he won't even follow up with me because I have nothing to offer him.

What's the point of coming to see me when I'm just going to tell him that he needs to eat
differently? He has heard that several times already. Why would this time yield different results?

Since becoming an investigator, this isolated incident became a much more common event for me. I got referrals from several of the other hospitals and systems in the area as well as referrals from four outside states.

That's how little success anyone anywhere has with treating this condition. Now, my patients with FCS has gone from 1 who won't come to see me anymore to about 8 who I am either the primary physician or consulting for across multiple states, including Mark, who you heard from, when he came to see me to try to get enrolled in the trial.

We weren't able to, as you heard before. I sent him straight from my office to the emergency room because of an acute episode of pancreatitis. Throughout my experience in the trial, I have seen platelets drop. I monitor them closely and I adjust the dosing as needed.

I'm happy to review the labs frequently
because I have seen my patients live without pancreatitis and their quality of life improves greatly when some of the daily symptoms and the fear of pancreatitis can be removed.

I have never seen a group of patients so eager to participate in a clinical trial for the hope that some of these pains can be improved. These patients are rare and the enhanced surveillance is something that, in my experience, physicians and patients are happy to adhere to because the alternative is completely inadequate.

The challenges that the medication bring up are nothing compared to the challenges that the physicians and patients deal with on a daily basis. Having an option, any option that can take away the pain of pancreatitis, the fear of pancreatitis, the daily abdominal discomfort, not to mention the social, cognitive, and workforce issues that happen when someone has FCS.

I'm advocating for the approval for volanesorsen so that these rare and incredibly difficult-to-treat patients have a single option to
try to improve their lives. Other difficult-to-use medications have been approved for diseases with similar frequencies in the population like homozygous FH.

Even HoFH, which has very high mortality, I would argue doesn't have nearly the kind of morbidity associated with it that FCS does. FCS patients have more frequent hospitalizations, have difficulty holding down jobs, and have more emotional and social dysfunction.

I would urge for approval of volanesorsen to give us the practitioners and the patients something to improve the treatment of this devastating condition. Thank you for your time.

DR. WILSON: Thank you very much. Next, we'll hear from speaker number 9. Please go to the podium, introduce yourself and any organization that's sponsoring you.

MR. TITLEBAUM: Good afternoon, everybody. Thank you for the opportunity to address the EMDAC open public hearing on this historic day for FCS patients. My name is Joseph Titlebaum and I am the
chairman of the National Pancreas Foundation. I live in Bethesda, Maryland.

The NPF is a national nonprofit that provides hope for those suffering from pancreatitis and pancreatic cancer through funding cutting-edge research, advocating for new and better therapies and providing support and education for patients, caregivers, and healthcare professionals.

I became involved with the NPF because my mother suffered from acute necrotizing pancreatitis and my father suffered from pancreatic cancer. My mother's fight with pancreatitis involved multiple surgeries at the George Washington University Hospital in Washington, D.C. and a 6-month extended convalescence at my home while we had infants.

I'm here today to speak a little bit about what it is to suffer from pancreatitis since the majority of FCS patients ultimately also suffer from pancreatitis. The NPF has no financial interest in the success of the sponsor's application, although Akcea has been a financial supporter of the NPF.
Pancreatitis, as you know, is a debilitating disease. It frequently triggers intense pain that leads to extended periods of hospitalization, preventing patients from eating regularly, working, or leading normal lives.

While some chronic pancreatitis patients have benefitted from new surgical endoscopic or other treatments, many others simply manage with regular hospital visits, pain medications, and dietary supplements that aid in the digestion of fatty foods.

Through my work with the NPF, I have gotten to know many patients who have learned to manage the terrible consequences of pancreatitis. Those who have endured multiple surgeries include islet cell transplants and others who are not candidates for a surgical cure and are forced to find a way to live with intense pain as a chronic condition.

I have learned to admire their courage in the face of adversity, but I believe we can do more to enable others to avoid this sort of debilitating pain and the intense social stigma that is
associated with having pancreatitis.

If there is a treatment that could avoid this sort of suffering among FCS patients, I think the treatment should be made available for all those who might benefit as quickly as possible. I find it hard to imagine that the risks associated with the new medicine exceed the costs and pain of having to live with chronic pancreatitis.

On behalf of the patients in the United States currently living with FCS, we urge you to vote to approve volanesorsen. Thank you.

DR. WILSON: Thank you very much. Next, we'll hear from speaker number 10. Please introduce yourself and any organization that's sponsoring you.

MS. SUTTON: Good afternoon. My name is Lyndsey Sutton and I am here on my own to tell you my story about living with familial chylomicronemia syndrome. FCS, you make my life so hard almost every single day. I cannot go an hour without stressing that, because of you, I am going to get pancreatitis.
I worry every single day about the symptoms you may bring and what impact you are having on my future health. The worst part is, I have grown so accustomed to feeling so crummy every day that I have forgotten that it isn't normal.

Even when I follow a strict low-fat diet, you are still unhappy and make me suffer pain and discomfort. You have succeeded in exhausting me. You scare me more than anything because you hold my health in your hands. I have been hospitalized more than 30 times, one bout landing me in intensive care for two weeks with triglycerides of 12,000.

My pancreas is 50 percent damaged from necrotizing pancreatitis and the thought of ever experiencing another bout is absolutely terrifying. What you just heard was from a letter I wrote to FCS two and a half years ago. This is a snapshot of my life living with FCS before I received volanesorsen.

I began taking volanesorsen over two years ago. Since beginning this treatment, I have not
experienced a single episode of pancreatitis.
Volanesorsen has been life changing. Many might
think that not having pancreatitis is the best part
of all of this, but that's just one piece of the
puzzle.

My quality of life has vastly improved and I
wish that the study questionnaire had allowed for
me to better express this. My day-to-day symptoms
are gone and the constant fear and burden of
getting sick after every meal I eat is non-
existent.

Of course, I still follow a nearly fat-free
diet and avoid alcohol, but it is for those moments
that I am on vacation or out with friends to a
place where I have few dietary options that I am
free to live my life without the severe
consequences.

It is no secret that volanesorsen is not an
easy drug to take and I have suffered side effects.
I have dosed over 100 times and have experienced
two terrible injection site reactions where my
stomach swelled up, became very tender, and caused
me to vomit.

I would undergo this time and time again if it meant that I would never have to experience pancreatitis or daily discomfort. That is how valuable this drug is to me.

A separate side effect that I have encountered is a minor drop in my platelet count and now I need to get routine blood testing every two weeks for monitoring. But again, if this means getting the drug, the risk is well worth it. My life before this drug was hard.

Due to the rarity of this condition, most people never experienced what I have experienced on a day-to-day basis. My quality of life was much lower than it should be for an adult my age. The fear of getting sick lurked and was almost worse than the actual case of pancreatitis because it prevented me from partaking in activities that I wanted to do.

Having said that, please know how life changing and beneficial this drug is for me. You know that, tomorrow, you are going to wake up and
be okay. Without this drug, I go to bed unsure if I will make it through the night without a severe case of pancreatitis.

Since being on drug, I do not question my future health, I have energy, I feel healthy. As I stand here today, after traveling 2,600 miles, I hope my story resonates with you. I have lived with FCS for 27 years and I am an expert.

Volanesorsen provides me with peace of mind and hope. Though there are side effects, they're minimal compared to the mental and physical pain I have experienced without this drug. I want you to know that I have been through unbelievable health challenges and can say firsthand that this drug is the best thing that's ever happened to me. Thank you for your time.

DR. WILSON: Thank you very much. Our next speaker is speaker number 11. Please introduce yourself and any organization that's sponsoring you.

MS. ALEXANDER: Good afternoon. My name is Lori Alexander and I'm the director of the Lipid
Center of Excellence at the Jacksonville Center for Clinical Research. I'm a clinical lipid specialist and a registered dietician/nutritionist.

I am here today speaking on behalf of the Foundation of the National Lipid Association to share our position that people living with rare diseases such as FCS desperately need treatment options. The NLA is a nonprofit organization of physicians, nurses, registered dietitians, exercise specialists, pharmacists dedicated to the signs of lipidology.

The Foundation of the National Lipid Association focuses on patient education, advocacy, and support of those with lipid disorders, including rare diseases such as FCS.

You've already heard quite a bit about the impact of FCS, the hypertriglyceridemia due to the lack of lipoprotein lipase and what these people have gone through. These people live at constant risk not only of severe pancreatitis, but all the other daily symptoms that you've heard about, not just physical symptoms, but all the cognitive and
emotional symptoms that go along with that.

This burden of illness really can significantly affect not just their physical issues, but also their career choices and many other social activities that you've heard about.

Because of the types of mutations in these people, many of the traditional lipid-lowering medicines do not work. This is very devastating for these people. Since they can't increase the clearance of triglycerides with LPL enzyme, they have to rely on increasing the production or decreasing the production.

Of course, this is very, very difficult because the only option they have is an extremely ultra low or 0 fat diet. They also have to avoid alcohol, limit severely simple carbohydrates and sweets, and as you heard, this severely limits their ability to enjoy life socially.

As a registered dietician/nutritionist, I can certainly attest to the difficulty and challenges these people experience in trying to adhere to the only treatment, diet, that is
currently available to them and hoping that it
actually helps them.

People with FCS need to limit their daily
intake of fat to no more than 10 to 15 grams a day.
One tablespoon of olive oil has 14 grams of fat.
This makes it very challenging for them to meet
their essential fatty acid needs and they often
require special supplements such as medium chain
triglyceride fatty acids, which do not increase
triglycerides, simply in order to meet their
nutrient intake and to meet their calorie needs.

These can be very expensive and challenging
to incorporate into their daily diets, but focus on
diet alone is not enough. Many people with FCS, as
you've heard, continue to experience pancreatitis
and many of the severe symptoms, even when they're
following close to a 0-gram fat a-day diet.

The medication volanesorsen offers hope to
these people. Clinical trials as you've heard are
very encouraging, showing a reduction of 60 to 70
percent of triglycerides in these people, which is
huge as standard of care medications are
ineffective for them.

This is very exciting for these people, many who have been struggling for years without adequate medical therapy. Like many of you, I'm a scientist and I can imagine if you try to put yourself in their shoes. This treatment could greatly impact the physical, emotional, and cognitive symptom issues that they experience.

I greatly urge you to encourage it to pass. Thank you.

DR. WILSON: Thank you very much. Next, we're going to hear from speaker number 12. Please introduce exactly what you're presenting because we've already heard from you. Thank you.

MS. SUTTON: Hi, my name's Lyndsey Sutton and I am speaking on behalf of Rebecca McFalls and this is her exact testimony.

"Good afternoon. My name is Becky McFalls. I haven't been reimbursed to be here today. I'm here on behalf of myself as someone who lives with FCS. I struggle with living with this rare disease and I want to share my story."
I struggle with it day to day and it has an impact on my dreams. I live every day not knowing if or when my next pancreatic attack will be. Regardless, I experienced pain, fatigue, xanthomas from my feet to my shoulders. There are days when I can't even do basic tasks that I should do; laundry, dishes, grocery shopping.

That burden falls on my husband who is also my caregiver. He also carries the burden of working two jobs to meet our financial needs caused by my disease.

Due to the frequent amount of hospital stays and with him working two jobs, he can't be there for me. It's hard on me. I'm fortunate, however. My mom picks up that slack. Again, I feel like I'm a burden.

But the burden of FCS on my family is more than day-to-day suffering. It has an even more profound impact. Growing up, I wanted a husband and children. I met the man of my dreams, my husband, Scott, but my dream of children didn't happen.
My high triglycerides made pregnancy dangerous for me for an unborn baby. I even gave Scott the option to not get married so he might have the opportunity for a family I couldn't give him.

Scott didn't take me up on that thankfully. He has been by my side for 10 years. The reason I came here today is to ask you to approve this drug. I'd like to try it. Low-fat, no-fat diet, exercise programs, yoga haven't been enough to lower my triglycerides.

This drug could mean less frequent ER visits and fewer hospital stays. That would be wonderful. It could be life changing. It could give Scott and me the opportunity to be more financially stable and healthier to be able to adopt a child.

It could give us a chance to travel and do things we want to do as close to normal as possible. I'd love to feel normal and not worry about having a pancreatic attack away from home.

Please give Scott and me that chance. Thank you."

DR. WILSON: Thank you very much. Next,
we'll hear from speaker number 13. Please introduce yourself and any organization that's sponsoring you.

DR. ZANGENEH: Good afternoon. I'm Farhad Zangeneh. I'm a clinical endocrinologist practicing in northern Virginia. And I'm here to represent AACE, American Association of Clinical Endocrinologists. I used to be on the board of directors. I'm a member of this association.

I'm making a statement on behalf of this organization. AACE has received funding from many pharmaceutical companies, including today's sponsor. And AACE is the largest organization representing clinical endocrinologists from 7,000 members, 97 countries, and mission of AACE is to enhance the lives of patients with endocrine diseases and to help the clinical endocrinologists with the latest state-of-the-art scientific information.

Now, with that said, everything is a story. So I have been actually here before for pio, lira, degludec, and as of late, PCSK9 inhibitors. So
thank you so much for allowing, as a clinical
endocrinologist, to have access to those therapies
so I can help my patients.

Someone said, because I think these codes
are just so invaluable, a physician once said the
best medicine for humans is love. Someone asked,
what if it doesn't work. He said and smiled,
"Well, I'll just increase the dose."

I wish it was that easy. So I had sent some
slides in, but it was just late last night and I
missed the deadline. And of course, this story
began with the fact that I did not know this drug
existed. I didn't even know how to pronounce it.
I didn't even know how to pronounce the name of the
company.

To me, FCS was a slide on Cleveland Clinic
Board Review, which I am a co-director. I did not
even have a patient for many years, up until a
month ago, where Bobby walked into my office.

This is his story, so really, it's all about
the patient. So the interesting thing is, as I sat
here and listened to the stories here, all the
stories are very similar. 44-year-old Chinese American, when he was a kid in kindergarten and had GI issues, no one knew what was going on. It was not until his mid-20s when he finished Marine Corps that they diagnosed pancreatitis.

Forty-five total episodes to date, 25 hospitalizations; I mean, these are stats you don't want to have. He gets married and his wife said, "This is not a life to have. Let's get things checked out." And basically, by the time they evaluate him, he has splenomegaly.

The head of the pancreas are removed and, of course, by this time, exocrine pancreas is destroyed to some degree. Endocrine pancreas is destroyed. They're in kind of a tailspin. He loses a lot of weight in a reactive way, 160 pounds, goes to 130.

You have diabetes now, insulin requiring. So he arrives in my office on insulin, so he has become an acquired type 1 on basal insulin and sliding scale, which are words endocrinologists do not like to hear.
He has now acquired hypoglycemia, which is pancreatitis on hypoglycemia, two of the greatest side effects that can ever impact the human body, the greatest equipment to ever walk the planet. So when we talk about side effects, everything in life is about risk-benefit ratio.

Anybody will cross the street and, of course, if someone says I have to monitor for platelets, and if you have to go to the hospital every week, you're getting monitored all the time.

So I think the point is that we really have to have a proportional response when we're dealing with something like FCS, very rare, but very, very impactful, so of course when he came to see me, his triglycerides were in excess of 6,000, 6,700. So on max niacin, 2 grams, max fenofibrate, max prescription fish oil, I changed his insulin to designer insulin. I got him carbohydrate counting.

He saw the best educator. He's got CGM. He's almost near bionics. A1c is beautiful. Triglycerides have dropped to 2,400. And as you know, fasting triglycerides of 2,400, you're still
in pancreatitis country and of added statins, window dressing, but still we are clearing 2,500 and no lower.

So again, that's the best that we can do. So he's still having recurring episodes. So again, I ask him to come today, but because of traffic, he couldn't make it. We were going to share time. And when I contacted AACE, I said, "Are you guys going to this meeting?" They said, "Yes, we are." I said, "Can I jump in?" And they said, "Yeah, we'll give you the time," and I said, "Because I have an actual live patient." This is actually a very good scenario because really, after all, this is about the patient.

I also want to thank my staff for staying later this afternoon because I'm kind of the last of a dying breed of NR1 clinical endocrinologists that are still trying to make it here. So again, if someone says this drug is expensive, of course it will be, but it's not for everyone. It is for someone who is on every medicine known to man.

Of course, lipoprotein lipase is under the
command of two hormones, hormone insulin, and
hormone thyroxine. Thyroid is normal and his
diabetes is perfect.

Then as I was driving, I said, "Well, you
missed coming in." He said, "Make sure they know
I'm not fat." He sends me his picture and he looks
like Bruce Lee. He is cut. He is built. Make
sure I'm not fat. So again, this is not exercise
and diet. And again, those are two words that
American College of Endocrinology does not like,
healthy eating and increased physical activity.

So this is, I mean, someone who's done the
very best he can. So I think the key here is, you
guys have access to things that you can protect by
doing extra safety. There is REMS. There is
additional testing.

So I think pretty much I know the mechanism
works on antisense. There is this thing called
common sense. And then there is this thing called
science. So I think, clearly, based on this
scenario that just dropped in my lap and the
patient, really, and hearing the suffering that
goes on here, our science is evolving to the fact
that we can help our patients correctly and deliver
a proportional response to the degree of suffering
based on physiology and biochemistry.

So thank you so much for your time.

**Clarifying Questions (continued)**

**DR. WILSON:** Thank you very much. The open
public hearing portion of this meeting has now
concluded and we will no longer take comments from
the audience.

Now, the committee will now turn its
attention to address the task at hand, the careful
consideration of the data before the committee as
well as the public comments. And I and the
committee really want to thank all of those who did
present and especially for some of you. We
recognize you are affected or you have family
members and you have personal stories.

We value that. That is part of this review
process. Some of you have not been to these
advisory committees before. We listen to you.
It's very important, what you contribute.
So the next is to finish with our questions from this morning. And I have a list of names and this was to follow up on, I believe, originally the sponsor's initial presentation. And I am going to go down the names.

Now, mind you, we have covered a lot of material since then. We will then recycle back so, when I read your name, if you can't remember your exact question, you'll get another chance.

Dr. Epstein? Dr. Yanovski? I'm sorry.

Dr. Epstein, did you have a question from the morning, from the sponsors?

DR. EPSTEIN: Yes. So in the CS6 protocol, we saw the exclusion/inclusion criteria. I was wondering why they didn't specify using the Atlanta criteria for pancreatitis. As we know, a lot of cases are pancreatitis or non-pancreatitis when we look at them if they don't follow that criteria. And that may have affected the robustness of the study.

The other thing is, I didn't see exclusionary for cholelithiasis,
choledocholithiasis, metabolic x syndrome, bariatric surgery. I didn't see bariatric status. There were a lot of things that were maybe not included in your presentation.

I'm just wondering, were those things actually in there, renal insufficiency, a non-dialysis-dependent renal disease, et cetera. Were they in the exclusionaries and how did you handle those? Because that would have a definite impact on your overall report.

DR. O'DEA: Thank you. To the first part, let me start at the inclusion criteria. So yes. Severe renal failure, severe hepatic disease were exclusionary criteria. Recent surgery, not distant surgery, such as you mentioned, were exclusionary criteria.

In terms of where I was going to start, which was the Atlanta criteria, we used the Atlanta criteria in our trial. We used what is commonly used in clinical trials, which is a modified form of the Atlanta criteria. Audience I know that Dr. Freedman can comment on that just to explain it
a little more if that's helpful.

But I think it probably is worth hearing because it is the gold standard, as you say.

DR. FREEDMAN: That's a good point. So the revised Atlanta criteria were used to adjudicate all the events, both retrospective as well as prospectively during the trial. And patients were given either -- if you met the criteria exactly, were definitive for acute pancreatitis versus probable versus possible or otherwise other --

DR. O'DEA: Did we answer it?

DR. WILSON: Also I think, Dr. Epstein, the question about the other exclusions --

DR. O'DEA: Yes. The other exclusions, I'm not sure I have a list of them readily available. But the top-line ones were severe hypertriglyceridemia from other causes, uncontrolled diabetes, i.e. hemoglobin A1c or greater than 9, a patient on plasmapheresis if plasmapheresis was an exclusion.

Active pancreatitis in the last number of weeks and a prior history of, as I mentioned,
severe cardiac renal or hepatic disease. They were the major exclusion criteria.

DR. WILSON: We didn't hear anything about alcohol intake, either, presented.

DR. O'DEA: All of our patients were on diet and of course diet alcohol is a core element of the FCS diet. And so that was a critical part of the dietary control of the patients, yes.

DR. WILSON: But were the patients excluded who were alcoholic or had been drinking regularly other than prior to the 6 weeks?

DR. O'DEA: Absolutely. These would be patients with secondary causes of hypertriglyceridemia. And just coming back to where we started earlier this morning, for us it was very important to define the population very well, to look at the population with the highest unmet need so that we would have the most appropriate and optimal benefit.

That did include genetic testing, did include LPL function as well as hypertriglyceridemia. So we did try to narrow the
beam to those patients who were most in need of treatment.

DR. WILSON: Can you explain how you got 750 and not 2,000?

DR. O'DEA: So 750 has been used before as a cutoff for entry criteria for patients in these hypertriglyceridemic trials. As was mentioned -- and I think it was Dr. Freedman, also -- 750 is also where chylomicrons or Dr. Rader actually predominate in the circulation.

So it really is the inflection point for the appearance of chylomicrons in the serum. We did mention that to the committee, we did measure chylomicrons actually themselves for all patients in the course of the trial. And they follow exactly the same pattern of reduction as hypertriglyceridemia themselves did.

DR. WILSON: Dr. Yanovski?

DR. YANOFSKI: My question was already answered.

DR. WILSON: No questions. Dr. Ortel?

DR. ORTEL: I asked a question before about
the characteristics of the thrombocytopenia.

   DR. WILSON: There was a question just
before lunch. Dr. Neaton?

   DR. NEATON: I asked the question for them
to consider at lunch.

Ms. McCollister?

   MS. McCOLLISTER-SLIPP: Hi there, a couple
of different questions. I'm not sure how to ask
that since I'm facing in the other direction. I
was curious about the connection or lack thereof,
apparent lack of connection between a decrease or
seeming therapeutic effect in terms of the drop in
triglycerides and a lack of change in abdominal
pain.

   It looks like there's a little bit more
nuanced data in the briefing book that was given to
us ahead of time. But based on the slides that you
presented this morning, there doesn't seem to be
much of a decrease in pain and I was wondering if
you had any sense of why that might be the case.

   Do we have any sense of sort of, in the
natural course of the disease, when pain starts to become present? My hunch is, people probably are not diagnosed prior to clinical symptoms or pain.

So that might not be a question that you can answer at the moment, but I'm just wondering if there's any sense of why that might be the case because this is probably going to be an expensive drug. It's going to be a difficult drug if it doesn't have a reduction in pain and quality of life and improvement in quality of life. Then I'm just wondering about the benefits.

DR. O'DEA: So you're correct overall in our trial and that may be a design issue on our part. We did not collect clear evidence that pain overall was positively impacted. We did collect evidence that patients who came into the trial with pain at the time they entered the trial had a reduction in pain.

Now, we only collected the most severe episode once per week, which was probably insufficient data gathering for a population as we just heard who have recurrent and chronic pain. So
that's the first thing.

The second thing is that we've actually gone back in part of our development of a disease-specific quality of life tool. We've gone back to the patients who participated in the trial and, among those patients we have asked those questions about whether or not, again, similar to the witnesses here, there was a subjective improvement in pain and our evidence suggests that we have subjective improvement in pain.

We did a statistical analysis on it. It is statistically significant. And we are moving forward, this quality of life tool, into full validation at the present time.

MS. McCOLLISTER-SLIPP: Second question is related to the recommendations for your REMS strategy. It seems like, as somebody who has to get, based on FDA risk guidance, the insurance companies tend to use that as gospel.

I take an expensive drug that requires monitoring based on FDA guidance. Essentially, insurance companies have a way of using that as a
block for people getting access to particularly expensive drugs. Have you anticipated that potential burden?

I mean, obviously, you want to make sure that people are safe and that they don't have severe side effects, but have you anticipated what that potential burden may be? And have you looked at or made any proposals for when that type of monitoring can stop, that there may be less of a need for that significant ongoing monitoring?

DR. O'DEA: So at the present time, we have patients who have had more than three years of treatment. We do not have a -- so let me just say, in our REMS program, we plan to continue the monitoring program that was shown this morning. We will continue to assess the patients.

We will be running two different ways in which we'll assess the patients. One is within the REMS, through enhanced pharmacovigilance, collecting information on events, but also through our global registry study, which will be run in the U.S. and other countries that we've been in, in our
clinical trials to collect more actively and prospectively information that will help to guide future advice to patients and physicians about the appropriate monitoring frequency for the platelet issue.

So at the moment, we don't have a new guidance. As was said this morning, we're making our guidance more conservative. Now, that doesn't mean that necessarily at the present time we're proposing more than every 2 weeks. And it's important to point out two weeks is the initial.

It's only if you're normal that your platelet count is measured every 2 weeks. If your platelet count is not normal, you go to a higher frequency of monitoring. But at the present time, adding the weight element -- and I know there's some controversy about whether that is fully protective or not and we're open to that consideration and discussion, but we do believe it's an important addition to add to the monitoring of patients.

MS. McCOLLISTER-SLIPP: Then monitoring
presumably would require either going to the
doctor, going to a lab, getting your blood drawn,
waiting for the results.

DR. O'DEA: So in our trial, we've had home
care, as was said by one of the physicians who
stood up. And I think Dr. Baum has said the same
thing. Patients come from four states. So they're
not coming to their specialist's office. They're
having home care.

We have initiated an arrangement with one of
the big national labs, not so much that it will be
a central lab, but actually a central data
repository. We're more concerned about having a
data repository so that we have pathways to
communicate with the patient, and caregivers, and
multiple other stakeholders in the process.

So that is part of what we're going to do.
And to your earlier point, I'm not really on the
business side, although I carry a business card.
And we are concerned to facilitate as much as we
can for the patient, access to monitoring as well
as communication and protections through both the
REMS, all of the other patients' support processes that we're putting in place, including potentially some support in terms of testing that may be needed to establish the diagnosis or any of the other things that will facilitate access to care.

DR. WILSON: Dr. Sinclair, did you have a question?

DR. SINCLAIR: In the ongoing open-label extension trial, what are the projected dates for the next analysis and the final analysis?

DR. O'DEA: So we have completed the efficacy trial CS6 and it is in reporting at the present time. CS7, which is the long-term 2 additional years of treatment, is no longer recruiting as of the end of last year.

So since patients can be in that trial for 2 years, it will be close to 2 years before we have the final report, but it's an open-label trial and, for that reason, we're following the data very closely. I get 12 e-mails a day with everybody's platelet count, so we know exactly what everybody's platelet counts are.
We know who's being notified of these counts and we know what actions are taken. And we have the opportunity to step in if we need to, if we feel that the appropriate action is not being taken.

DR. SINCLAIR: So the analysis would be, the final analysis was projected?

DR. O'DEA: So it would be the end of 2019.

DR. SINCLAIR: There's no interim analysis planned between now and then?

DR. O'DEA: No formal interim analysis, but as I said, it's open label, so we're able to see triglycerides. We're able to see platelet trends.

Yes.

DR. WILSON: I think we're now going to move towards the questions that came up just before lunch and start off with Dr. Kane. I apologize. If you can remember your specific questions, we had a whole series and then I close it, and then we'll hear from the sponsor.

DR. KANE: Yes. You can guide me. I have the questions that I left with you before lunch. I
do have additional questions both for the sponsor
and for the FDA. You just let me know when you're
ready for them.

DR. WILSON: So what we're going to do is
try to go as efficiently as possible for the
sponsor and then we're going to go to the FDA. And
then we're going to go into open discussion, so
that's our sequence from this time forward. Okay?

DR. KANE: I may use this, then, to lead
into the whole series of questions that I have. I
want to say, first of all, that I think the sponsor
needs to be acknowledged for the efforts extended
for this very rare condition to enroll and have
some 40 world sites. I think that's a pretty
enormous effort.

I do want to make a comment first also. In
the public session, I think this was very, very
informative, but it seems to me that the
experiences that we heard were not quite the same
experiences in the population that was studied in
the trial.

Now, I'm trying to understand that a little
bit better. One of my questions just before lunch was the observation that I had both in some data from CS6, CS7, and CS16. And it looked to me from 20,000 feet or so that the effect of an every-other-week administration was, I'll say, similar to the effect on triglycerides of every-week administration.

I'm thinking with respect to both efficacy and safety. So I wanted to ask the sponsor, doesn't every other week get you close to where you are with every week?

DR. O'DEA: So you are correct. And of course, this is a post hoc, to be quite honest, observation. And patients did segregate on a weight basis. I think that's very important just to remind everyone.

So for patients who are in the lower dose because of the slightly lower body weight, on average we have about a 60 percent benefit compared to the 77 percent that you saw in the overall data.

So we do have about a 15 to 20 percent difference between the 300 milligrams every 2 weeks
and 300 milligrams once a week. So one could argue that 60 percent is an adequate benefit. In the case of our initial treatment plan, we were looking to optimize the benefit given the severity of this disease.

As we heard, there were values of 10,000, 8,000, and 77 percent seemed like a better number to target.

DR. KANE: Thank you. And if I can say also, very brief answers will satisfy me very well. Thank you. In your slide CO-47 to follow up with this, then, you in your graph, showing the blue completers, have dose reduced, but if I understood it right, it wasn't a reductional dose. It was an increase in the time interval.

DR. O'DEA: That's correct, every two weeks.

DR. KANE: That's fine. That's fine. And may I continue, then, with my series?

DR. WILSON: How many more questions do you have, just in the interests of moving forward?

DR. KANE: It's brief questions that have brief answers. I want to be sure, first of all,
with the specific patients with FCS that have been studied and described, I think we're talking about 56 unique patients as of the August report.

DR. O'DEA: So obviously, the FDA count the numbers differently. We count 66. 1 patient did not meet and that was, in retrospect, for technical reasons either a qualification of genetics or --

DR. KANE: I was adding to gather the patients who received drug treatment either in 6 or 7.

DR. O'DEA: Yes. You're correct. I'm sorry.

DR. KANE: Now, the next point I wanted to get to is that you have, I believe, in total 8 patients who had severe thrombocytopenia, platelets below 50,000. And if I looked at the CS6 and CS7, we had 6 in total below 50,000.

If I added the patients who received drug in CS6 and the 43 who were de novo in CS7, we have 76 individuals and 6 of whom severe thrombocytopenia. Is that correct?

DR. O'DEA: That's correct.
DR. KANE: The next thing I was looking at then both in the graphs that the FDA provided -- and I realize that there were varying time intervals that were being applied to these observations for these patients, but I think that we do have some evidence that, for some, there was a quite precipitous drop in the platelet count, and then a variable recovery time after that.

So what I was trying to understand, then, if you were measuring every 2 weeks a platelet count, how sensitive would that be to detect a precipitous drop. And I don't believe I understand that or have a good enough view of that from the information that we have here so far.

DR. O'DEA: So I do have a slide that I think will cover all components of your question.

DR. KANE: I have a couple conceptual questions that perhaps could be answered briefly if you allow me.

DR. WILSON: If they're conceptual questions, perhaps they could wait until we get into joint FDA plus the sponsor. Let's try to get
through these, especially when we might need data because then we don't have directed data questions. Okay?

DR. KANE: Thank you.

DR. O'DEA: So in answer to your question, we looked at the rate of decline from 100,000 down to the lowest value measure for each individual patient. We looked at the time to recovery to 140,000 and we looked at the time during which the patient resided in that, sorry, high-risk low-number range.

So if we look at the time that the patients resided in that severe thrombocytopenia range, they were between 3 days and 6 days. So that was the period of time that they had values less than 50,000.

In terms of the way down, the range was 102 days to about 15 days, on the way down to 50,000. And the recovery time to normal ranged from about 4 days up to about 40 days.

DR. WILSON: Can we move forward?

Dr. Ortel, did you have a question for data
clarifications?

DR. ORTEL: Yes. I had two questions. One was focused on the quality of thrombocytopenia. And by that, I mean, were other cell lines affected, what do the red cells look like, was there thrombocytopenia, what were the characteristics of the thrombocytopenia.

That drives into the second question because a number of these patients, it sounds like, when they get to severe thrombocytopenia, they are treated with other things, not just withdrawal of the drug. They had listed they were getting intravenous steroids, they were getting IVIg.

These are not necessarily benign treatments and, if the hematologists to whom these people get referred doesn't quite know what the mechanism of the thrombocytopenia is, these patients may get inappropriate treatments. And I was wondering how were you going to try to educate the hematology community about what to do with these.

DR. O'DEA: Yes. So if you don't mind, for the first question, I'll ask Dr. Scott Henry to
respond as regards to work we've done on the other
cell lines and then also Dr. Sandy Shattil, who's
our consulting hematologist, who studied each one
of these patients, will comment on the use of
steroids.

It's an ITP protocol that we follow.

DR. SHATTIL: [Inaudible – off mic]

University of California at San Diego. With
respect to whether blood cell types were affected,
in the patients who developed platelet counts less
than 50,000, there was no change in white count.
There was no change in hemoglobin levels.

The peripheral blood smears that were
available by report did not show any red cell
fragmentation or spherocytosis. And in 2 patients
who had bone marrow histology examined, cellularity
was normal, including megakaryocytes. That's the
information we have on that.

With respect to the treatment, I share the
committee members' concern about potential
overreatment of grade 3 thrombocytopenia in
particular. And in looking at the treatments these
patients received at the discretion of the investigators, a short course of corticosteroids was administered to some, but not all of these patients.

One patient received IVIg and some patients recovered with no specific treatment. The label will include an indication that hematologist, presumably an expert hematologist, will be consulted when there is either grade 3 or grade 4 thrombocytopenia. Hopefully, overtreatment can be avoided and specific necessary treatment administered.

DR. WILSON: Are we resolved on that to move forward? The next data in query was from me. It was relevant to a slide by the sponsor, 58, and we have an estimate of effectiveness for pancreatitis, reducing the risk, and the question was, if there was a trial, how many people would it take and for how long, number of persons or number of person-years of exposure to potentially show that this molecule can reduce risk of pancreatitis?

DR. O'DEA: Dr. John Balser, our consultant,
statistician, will address that if you don't mind.

DR. BALSER: John Balser. I'm a biostat consultant for Akcea. What I'd like to do actually is address two questions at the same time if that's all right because Dr. Neaton actually asked the question about the enrichment for pancreatitis in the study, CS6, and did we have an anticipated rate of pancreatitis that we might have seen for the placebo patients.

I think that's actually directly related to this question and in fact is proper to position it as a rate, not a frequency. As my statistical colleague at the FDA pointed out, a frequency analysis is not really appropriate if you've got a different duration of observation.

So what I'd like to do is actually show you the rates that we actually calculated, but first let me address Dr. Neaton's concern and/or question. We had anticipated approximately a rate of .2 incidents per patient-year because that's roughly what we see in the literature actually between .2 and .35.
On that basis, we would have expected somewhere between 5 and 8 placebo patients that have had pancreatitis on this study. We didn't see quite that many, but what I can show you is what we actually did get.

That's going to be related to the question of study design. So what you can see here is, we did calculate the rate of pancreatitis events both for volanesorsen and placebo patients. The bottom two rows actually give what we believe would be the proper rate, which is based on total duration of observation, which was 29 patient-years for volanesorsen and 31.8 patient-years of observation for placebo.

But what you can see is the incidence rates per patient-year of observation, .03 in volanesorsen and .12 in the placebo group, on the basis of this kind of information, it would require a very, very large number of patients. As you know, this is a very rare disease and pancreatitis is a somewhat rare event historically.

So on the basis of this, we actually would
have calculated somewhere well in excess of 400 patients in a 1-year trial. We don't think that's a feasible study to actually conduct. But again, it is based on rate. It's not a frequency type analysis.

DR. WILSON: Yes. Dr. Neaton?

DR. NEATON: Can I just follow up on this a little bit? I mean, this relates in my mind to some of the other discussion around the whole target population that you're seeking an indication for.

DR. BALSER: Sure.

DR. NEATON: It's because the indication that we saw earlier today was very broad and didn't include anything about the history of pancreatitis. And so if you put the slide back up that you just showed, that's a starter.

So presumably, what you're doing here is, you're counting person-years of risk irrespective of taking treatment.

DR. BALSER: I'm sorry. I don't know what you mean by irrespective of treatment. We've got
two columns.

DR. NEATON: I'm looking at the next-to-last row, the total duration of follow-up.

DR. BALSER: Yes.

DR. NEATON: So basically, what the FDA statistician pointed out appropriately, is that the odds ratio of .31 was likely way overestimating the potential benefit because the duration of treatment was different for the study drug compared to placebo.

So as I recall, his rates, the rate ratio, would have been something like .82 compared to your odds ratio of .31. And so I don't understand the duration of observation here because that must imply you're discounting all person-years of observation irrespective of whether the person was taking treatment. Is that true?

DR. BALSER: I think you can actually see both because the two rows above that actually are normalized or adjustment for duration of treatment. In fact, the proper analysis into some ITT analysis would be based on patient-years of observation.
DR. NEATON: Yes. If you were following actively and appropriately everybody for pancreatitis, that's true. And that's another question we'll come back to, but even the row above that, I believe, perhaps we could ask the FDA statistician to comment, get this straight for us, is different.

DR. BALSER: Yes, sorry. I do need to point out that this observation does include observation for incidence of pancreatitis. Patients were followed. In fact, there's only 2 patients out of the entire set of volanesorsen patients who have less than 24 weeks of observation follow-up for pancreatitis.

DR. WILSON: So also here, have you made these calculations for persons who have already experienced at least one episode of pancreatitis in the trial?

DR. BALSER: Yes.

DR. WILSON: Yes, because this is all-comers versus 33 and 33, but there's a smaller number who have a higher risk because they've already
experienced one episode of pancreatitis prior to
ever being in the studies.

DR. NEATON: Maybe we can put up slide 51 in
your presentation. I mean, the rate's on here, but
I guess I was surprised -- these are very small
numbers -- not to comment on the subgroup analysis
per se, but kind of from the discussion that
motivated this trial in the study as well as the
public hearing, there were only 11 people in this
study that had more than 1 event in the past 5
years?

DR. O'DEA: That's correct, but 78 percent
of the patients had an attack of pancreatitis at
some point.

DR. NEATON: So you excluded apparently then
large numbers of people with this condition with
chronic pancreatitis. Is that true?

DR. O'DEA: No. I'm not sure how one makes
that --

DR. NEATON: I just don't understand why
these numbers are so low, why 11 out of 66 with
only more than 1 event in 5 years. It just seems
like the target population here is not enriched
like you thought it was.

DR. O'DEA: So this is a population in a
trial who were very well curated, who were being
followed very closely, and who were adhering to
diet. So one might expect the rate to be slightly
lower than you might find in the open community.

So there's only one natural history studied
and it looks prospectively at the rate of
pancreatitis in this population. And they come up
with a number of 1 attack every 4 to 5 years on
average for a patient.

DR. WILSON: Yes. Dr. Epstein, you had a
point to make?

DR. EPSTEIN: Yes, two points about that.
One, these patients in the placebo; did they meet
the Atlanta criteria strictly for pancreatitis or
were these just people who were told they had --

DR. O'DEA: These were curated. Sorry. All
of these, the retrospective, the 5-year look back,
and the on-study were all curated by the same
independent committee against the Atlantic
DR. EPSTEIN: To Dr. Neaton's point, with this being a different population than what we're hearing from these folks over here, did you study the xanthelasma, the retinal changes? We didn't hear anything about what's happening to their overall condition.

You've got some of these patients on it for a year. We'd expect to see regression of those secondary signs and symptoms. We didn't hear anything about that and it just makes you wonder.

DR. O'DEA: Right. There was only 1 patient with active xanthomata at the time they entered the trial. About 25 percent of the patients had had xanthomata, but the majority of patients had not had xanthomata in the past. We did do serial fundoscopic examinations in the population.

We did not have enough data because lipemia retinalis was not seen in enough patients for us to be able to deduce that we had an effect, but we did have the effect on serum triglycerides and, at the end of the day, the most important thing for the
patients, I think, as we've heard, is the avoidance of risk by reduction of triglycerides.

So I think we're able to deliver a substantial reduction in risk to the population and we do think that these data on triglycerides; CS16 without any filtering of the data -- we showed a statistical reduction. Now, it was not a pre-specified analysis, but it was statistically positive.

In this look back analysis, in those at highest risk, we did see a statistical benefit and overall, in the CS6 population, we had 4 events in placebo and 1 event on active treatment at a very different triglyceride level.

So we do believe that there's certainly at least a numeric if not a significant impact on pancreatitis. And I think, as we've heard from patients today, they've had a period of pancreatitis re-existence while on treatment.

DR. WILSON: Dr. Smith from the FDA, you wanted to make a comment?

DR. SMITH: I'd like to walk back a bit to
Dr. Ortel's question. He was raising a question about mechanism of the platelet reduction and the appropriateness or potential inappropriateness of therapy with steroids or IVIg. And I was wondering if you could clarify maybe for us in the committee what your current recommendations are in your open-label trial regarding steroid use in patients who develop platelet counts less than 50,000.

DR. O'DEA: So our current practice is the same as our proposed label, which is any patient who reaches a value of 25,000 or lower should be treated with steroids. And any patient who reaches 25,000 or lower should also have a hematology consult on recovery to ensure that there's no secondary reason why this may have occurred.

DR. SMITH: Right. So the hematology consultation was mentioned, but to Dr. Ortel's point, your current recommendation is for the use of steroids in patients with very low platelet counts. Correct?

DR. O'DEA: That's right.

DR. WILSON: We have one more comment, I
believe. Dr. Cuaresma? I apologize for
mispronouncing your name.

MS. CUARESMA: It's okay. You can continue
calling me doctor as well even though I'm not.

DR. WILSON: I apologize for that, too.

MS. CUARESMA: Thank you.

DR. WILSON: It's honorific today. What can
I say? But please go ahead. You had a comment and
a clarification you wanted. Thank you.

MS. CUARESMA: Yes. The FDA slide had said
that a single dose at 300 milligrams injection
lasts 24 hours. So I guess the question is, if the
life or half-life is less than a day, I guess I
just don't understand why the injections are every
week or every other week and how that affects the
chylomicrons' breakdown until the next dose.

DR. O'DEA: Right.

DR. REN: I can answer this question because
it's from my slides. So go to my slide number 3.
So let me rephrase the question. The question here
is saying there could be a paradox, which the drug
concentration in the blood is pretty much all gone
at the end of the dosing day.

How can the triglyceride reduction effect be kept for one week? Because the dosing regimen's once a week. So the answer is that I just need to show the table.

DR. WILSON: Keep advancing.

DR. REN: Yes. So where did drug go? It disappeared from the blood and it's not excreted from human blood. It's accumulated in the peripheral tissue, such as in the liver, such as in the bone marrow here, and in some other tissues.

The drug target is apoC-III mRNA. And which organ is responsible for producing apoC-III? It's the liver. So the drug is in the liver, highly accumulated. And even if the blood concentration is gone, you still have a lot of drug in the liver, still doing its job.

MS. CUARESMA: Thank you. I have another timeline question that kind of ties in with that.

DR. WILSON: Go ahead.

MS. CUARESMA: Thank you. So the other question again has to do with timeline with
triglycerides. It shows it at 77 percent of the 3-month mark and then at 55 percent at the 6 and then I think down to 44 percent at the 12-month mark. Why is there such a discrepancy and why are those percentages -- is the body resisting it at that point, at 12 months?

So although it says 77 percent reduction, it looks like, over time, that's half of that in a year. Does that make sense?

DR. O'DEA: So it does. It does. So what we're looking at is, we're looking at the compounding effect of some patients staying on the same dose, some patients having a reduced dose through a change in the frequency of administration, and some patients discontinuing treatment.

So when all of those are put together, there's a reduction in efficacy. But if you stay on one dose, whatever that is, whether it's weekly or biweekly, you have the same persistent triglyceride value. So it's still 70 plus percent at the full dose and it's 63 percent or so at the
half dose.

MS. CUARESMA: Thank you.

DR. WILSON: We have a few more questions.

Dr. Weber, you're up.

DR. WEBER: Thank you. For the sponsor, just before I ask the question, I'm trying to get my mind around the pancreatitis rate in the trial and reconcile some of the observations that we had from the higher study subjects in the public hearing.

First question, do all the subjects, prior subjects in trial know their study assignment at this time?

DR. O'DEA: They do.

DR. WEBER: I guess the question I had was, in terms of the rate of pancreatitis per patient-year, do you have data on the rate before the trial for placebo versus the trial and whether or not there was a significant reduction in the rate of pancreatitis such that there was a study effect that was independent of the drug?

DR. O'DEA: So we do have that. That is
reported in our overall data. I don't believe I have already made a slide with that. The analyses we did were in the higher group, those who had more than 1 attack, because 1 attack over the 5 years is an expectation. More than 1 attack is not an expectation and that's why we did the analysis on that group.

We had, I think, 17 attacks in 4 patients in that period of time. Overall, perhaps, I don't know if we have such a slide. But I can provide you with that information a little later. But let me see if I have it.

DR. WEBER: Sure. I'm just trying to clarify if there was a study effect that's confounding some of what we're seeing with regards to the --

DR. O'DEA: I understand. Understand.

DR. KANE: Could I follow up with Dr. Webb's question just to clarify further?

DR. WILSON: Please identify yourself.

DR. KANE: Robert Kane. Dr. Webb's concern was the post-study knowledge of this treatment
augmentation. But I think we should recognize that my reading of this; the majority of patients, some 80 percent, who had injection site reactions would know what their treatment was on study. Thank you.

DR. WILSON: We also had a comment from Dr. Low Wang.

DR. LOW WANG: So I have a question for the sponsor and a question for the FDA. And so the question for the sponsor is just going back to the rationale for not testing this drug in pediatric population, just thinking about the fact that when patients develop pancreatitis for the first time, we think that they have a higher risk for developing pancreatitis down the line.

So the utility of using this drug in adult population versus pediatric population is the horse out of the barn already. I think, from the open public hearing, it sounds like there are still a lot of repeated episodes seen in the adults, but could we prevent that by using this drug in pediatrics. Well, let me stop there.

DR. O'DEA: So we do have a plan for
pediatric development of the drug, of course. As was mentioned, it may take a long time for patients to be diagnosed. That's not necessarily true in every country. There are countries where there are concentrations of patients and they're diagnosed at a very early age.

I think we heard somebody was diagnosed in their first few years of life and that's not uncommon. Nursing children can be diagnosed with this disease as a consequence of mother's milk.

So it can be diagnosed at every age. We do have an active plan, as I say. We are initiating our trial around the world in the same countries likely that we are currently involved in and we will have a solution for the pediatric population.

We have a different dose paradigm in terms of scaling. We have learned and we do include our learnings into our subsequent studies.

DR. LOW WANG: Actually, if I could just --

DR. WILSON: Do you have a follow-up? Go ahead.

DR. LOW WANG: It's slightly different, for
the FDA. So this is for Dr. Roberts and this is in
the clinical review, slide 35. Now, this was a
slide that showed the platelet count of patients
who had episodes of epistaxis and petechiae.

So what I was wondering; these are the
platelet counts at the time of those events, but is
there any analysis of what happened to those
platelet counts later. Like, did any of those
patients experience later drops in platelet counts
after those events? Do we know that?

DR. ROBERTS: I don't think that we have an
analysis of what the platelet counts did after
these events. These were the previous platelet
counts right before the bleeding event. And I
don't believe we have one for what those platelet
counts did afterwards, although we do have patients
that did have very low platelet counts, like 8,000
that did have epistaxis and petechiae, but I don't
have a slide that shows that.

DR. SMITH: This is Jim Smith. We did look.
And it just made too busy of a figure, so I don't
think we actually have it to show the committee.
We looked at the platelet count immediately before those events as well as the next platelet count immediately after those events to get a sense for whether or not the event could have been a premonitory sign of a precipitous drop.

As I recall, in really none of the cases did we have a precipitous fall after that particular event.

DR. WILSON: So to follow up, Dr. Smith, the point was, were individuals who had a bleeding event or had the very low platelet count. It seemed to me, from what we've seen so far, they were on a trajectory to go low and then they still got another dose. Is that fair to say?

I guess I'm sort of following up on the earlier question. Can you predict that they're headed low and they're going lower? Is that fair to say or no?

DR. ROBERTS: I think it's difficult to predict. I mean, there are examples where they had 12 doses and they were below 50,000.

DR. WILSON: So that does not resolve it.
So the next part; let me tell you the rest of the afternoon. We'd like to finish on time. We have lots of discussion questions. We have not followed up with the FDA presentation from this morning.

What we'd like to do is to move to the FDA clarifications as the next step, but go through that rather quickly for any clarifications, so we can move into our discussion.

The discussion will still be able to involve the sponsor and FDA, but are there any pressing clarifications from the FDA, especially related to things? We'd like to have everything pretty much on the table when we get to discussion. So yes. Go ahead, Dr. Kane.

DR. KANE: Thank you. Kane. With regard to the REMS proposal, I wanted to understand, is there an experience to date with another REMS that has some of these characteristics such as every-week blood counts, 1-month dispensing of drug supply each month to the patient, and the consistency of getting reports every 90 days with regard to the treatment experience? Thank you.
DR. LaCIVITA: So there is some experience with these different elements. They're not exactly the same REMS. There are some REMS that are comprised of some of these elements, so there is a REMS that's currently approved with a 90-day status form and that is more event driven to find out if certain events were occurring and if monitoring was occurring.

There are REMS that are approved that require a lab value prior to dispensing the drug and the 30 days is something that the sponsor has proposed. We haven't discussed that within the agency and it's more than likely related to a month worth of insurance coverage. Does that answer your question?

DR. WILSON: Dr. Morrato?

DR. MORRATO: Elaine Morrato, a question for Dr. Roberts, clarifying on her slide 29, looking at the platelet counts over time.

DR. WILSON: Which presentation, Dr. Morrato?

DR. MORRATO: Her safety one, the clinical
review, Roberts's clinical review. It would help
this one. It says 29 on it.

DR. WILSON: Number 29 is the one with the
red dot. There it is.

DR. MORRATO: I thought this was very
interesting and I'm trying to reconcile it with, I
think it is, the equivalent of the slide from the
sponsor 66, which Dr. Budnitz kind of was also
asking about.

The sponsor's looks like the mean over time
is over 150. You're reporting a median of 122.
Can you just help me understand how are these
different if both of them are looking at platelet
counts over time? These seem to be dropping a lot
more than what we saw in the sponsor's mean counts.

DR. ROBERTS: I mean these are all of the
platelet counts, both planned and unplanned, so I'm
not clear on if that is the difference or not
between the two. And this figure would include
patients that are on drug and off drug as well. So
there's differential time on drug here, so that
someone may have gone off treatment.
There's two very low clusters of patients. Their follow-up platelet counts after that are not on treatment and I don't know if that's maybe from the --

DR. MORRATO: Was incorporated into the sponsor's slide, but all of that data would be in your slide.

DR. ROBERTS: Yes.

DR. MORRATO: Very good; then one just general question that might be helpful, since I know the discussion we're going to have to do to weigh two different life-threatening events. And you see these kinds of things looking across drugs at the agency. Can you help ground us with maybe the best estimates of the clinical consequences of these events?

So we saw some reports in the briefing documents about mortality or hospitalizations associated with pancreatitis. And what would it be for drug-induced thrombocytopenia? Are they comparable rates of mortality?

DR. ROBERTS: I would maybe refer to my
DR. DE CLARO: My name is Angelo de Claro. I am the acting deputy director of the Division of Hematology Products. We were consulted to comment on what would be the risks for bleeding in this case. It's very difficult to make that assessment, given the small safety database, and traditionally and without clearly understanding the mechanism, I think it's difficult to really state what would be the risk of bleeding, given the degree of thrombocytopenia that was observed.

DR. MORRATO: Right. In general, everyone is expressing concern over the risk. I'm just trying to get a sense of what's the likelihood of a really bad outcome when we say life threatening. Is it 1 in 100 of these cases? Is it 1 in 1,000? Is it rarer, more common? How do we in general for other drugs?

DR. DE CLARO: It varies from drug to drug and also concomitant medications. I know perhaps, Dr. Ortel, would you surmise a range in this case?

DR. ORTEL: Yes. It is very difficult to do
that, but you can argue, from other kinds of thrombocytopenias, let's say it's only the platelet count that's low. There's nothing else wrong. Usually, you don't have to treat a patient until they get below 30,000.

The risk of spontaneous bleeding does not really begin to go up until you get below 10,000. That's why I'm very concerned about the recommendation to give steroids for thrombocytopenia without necessarily getting a hematologist involved because it may not be indicated at all.

DR. MORRATO: What's the mortality risk? I mean, does everyone recover?

DR. DE CLARO: You can bleed anywhere and it can be fatal.

DR. MORRATO: Right.

DR. DE CLARO: You could bleed in your head.

DR. MORRATO: Right. But is it very rare?

DR. DE CLARO: Once you get below 10,000, the risk begins to go up. Once you approach 1, those patients actually --
DR. MORRATO: So is it 1:1? Like, once you get below that, you're 50 percent chance of death, 100?

DR. DE CLARO: I don't think that we have enough data that I can tell you exactly a percentage on that, but it is high enough that, once you get below 10, you do have to initiate some kind of treatment.

DR. MORRATO: Yes. But the reason I'm asking -- and there may be more for discussion -- is I worked on drug development that had severe agranular cytosis. And we had a lot of discussion around what does the seriousness mean and the consequence in today's modern medicine.

Maybe the death risk is much, much lower than earlier data reported decades ago and I'm just trying to get an anchor point with this because we're having to compare and trade off, so thank you.

DR. WILSON: So Dr. Shamburek, you had a follow-up?

DR. SHAMBUREK: Somewhere in my notes, I
have that when you looked at actually the bleeding
AEs, most of them occurred with platelet counts
greater than 75,000 and it was suggested that this
suggests a platelet function rather than the
number, which kind of makes the number a hard thing
to deal with.

DR. WILSON: So Peter Wilson here. Also as
a follow-up, I was wondering about other
medications that patients may have dropped in on
that can cause thrombocytopenia. And some of the
most common are acetaminophen, NSAIDs, and aspirin,
which we've not heard about at all today.

Presumably, that would be part of a REMS,
but is there any data up until now even for those
drop-ins or medications that may have affected the
metabolism of the drug itself, actually what was
administered? Yes, Dr. Ortel?

DR. ORTEL: So I was going to follow up on
that. The one person did comment on animal data
that qualitative platelet defects were not seen.
And I don't know what they've got in humans as far
as whether or not there are any qualitative defects
on top of that.

   Obviously, if you're taking aspirin, if
you're taking NSAIDs, and things like that, you can
have a qualitative platelet defect on top of that
which can modify that risk of bleeding.

   DR. WILSON: Thanks very much. Dr. Neaton,
did you have one other question?

   DR. NEATON: I had a two questions for the
FDA. One, I just want to say I thought Dr. Cambon
did a nice job of addressing a concern that I had
this morning about the counts that were showed
about pancreatitis.

   Slides 50, for example, and 51 showed the
counts on treatment. And so he did an analysis
which took into account the time on treatment,
which is very different for the two groups, and
showed that they're much more similar. The rates
from his presentation were .11 and .09.

   So then Dr. Roberts talked about adverse
events and I just wanted to ask her, if you apply
the same thinking to the adverse event summarize
that you showed, is it a fair assessment that we're
probably underestimating the difference in adverse event rates between the active treatment group and placebo group here?

   I mean, actually, Dr. Ren made a comment that I think is valid just when it comes to the median kind of platelet levels. The more often the nadir platelet levels, the more often you measure platelets, the more likely it is you're going to find a low one or a high one.

   It's going to influence a lot of the analyses, the differential follow-up in my mind.

   DR. ROBERTS: Yes. I mean, I think that it could. We did look at all of the adverse events whether they were on treatment or not, so from the beginning of the study all the way to the end of the study.

   But you're right. If you did discontinue and you weren't being followed up for adverse events, then yes, you might have be missing adverse events.

   DR. NEATON: Not only missing the numerator, which I'm still a bit concerned about, it's
basically the denominator.

DR. ROBERTS: Right.

DR. NEATON: Because the analyses that were shown on adverse events were largely adverse events while people were taking therapy and so that was a shorter period of time for the active drug versus placebo.

DR. WILSON: So what we're going to do next --

DR. NEWMAN: Can I ask another question?

DR. WILSON: Do you have another follow-up on that?

DR. NEWMAN: I have a clarifying.

DR. BUDNITZ: Dan Budnitz. Just to follow up on Dr. Neaton's point, I think the thing that's so critical about this point is that, because the dropout rate was so high and we don't have to think about this in most studies, with a dropout rate much lower, but I think halfway through the pivotal trial, I think I saw that a quarter of patients were no longer on study therapy, so for half the trial, a quarter of the patients were not on
therapy.

So it changes. Maybe you want incidence
density for these kind of adverse event rates.

DR. WILSON: Dr. Sinclair, I'm sorry. No?
Dr. Newman, I apologize. You had your hand raised.

DR. NEWMAN: It's me. I have a question for
Dr. Roberts. It was mentioned in the briefing
document that, with other antisense
oligonucleotides, there was a cerebral bleed in a
patient. How should that influence our thinking
about this product?

DR. ROBERTS: I think it just highlights the
risk associated with thrombocytopenia. So that is
something that we consider when we see these low
platelet counts that we haven't seen a serious
clinical bleeding event. But as was said earlier,
when you have very low platelet counts, your risk
goes up for having a major clinical bleed.

DR. KANE: May I just clarify? I think you
just used the wrong word there. We haven't seen
serious adverse event. We haven't seen major
bleeding, but we've seen serious adverse events.
Questions to the Committee and Discussion

DR. WILSON: I think are we pretty much done? We can come back for more clarifications with FDA or the sponsor, but we do need to get our work done, which is open discussion. And so we're now going to proceed to the questions of the committee and the panel discussions.

I'd like to remind public observers that, while this meeting is open for public observation, the public attendees may not participate except at the specific request of the panel. So first, we're going to, I believe, pull up question, discussion number 1, and I'm going to read this.

Partly, it needs to go into the record for the recording. A reduction in fasting triglycerides has been accepted by FDA as an endpoint that can establish efficacy for several classes of drugs intended to treat patients with severe hypertriglyceridemia, greater than 500 since lowering trigs in this setting is expected to reduce the risk for acute pancreatitis.
In trial CS6, patients with familial chylomicronemia syndrome or FCS assigned to volanesorsen, 300 milligrams weekly, exhibited a 77 percent reduction in triglycerides at month 3 on average in comparison with an 18 percent increase among those assigned to placebo.

That was significant p less than 0.0001.

When efficacy is established via an effect on a surrogate endpoint, however, uncertainty generally remains regarding the magnitude of the drug's effect on clinical benefit such as how patients, feel, function, or survive.

The expected type and magnitude of clinical benefits are important to consider when making a benefit-risk assessment. We are asked to discuss the efficacy, clinical benefits of volanesorsen in patients with familial chylomicronemia syndrome.

As you can see, there's A through E. This is a five-part, so I'm going to read A first and then we're going to discuss. And these are not voting. And then we're going to try to move rapidly through the different topics. And each
time, I will say, can we move on to the next letter.

Then at the end, I'm going to try to summarize all of what we've done. So first, A, has the applicant adequately characterized the effect of volanesorsen on triglycerides to inform labeling despite the proposal of a dosing strategy that has not been studied in clinical trials.

So we're open for a discussion. Raise your hand to be recognized and then we'll go through the individual discussion points. And I'll be taking notes and then, once we close each of these and then we come back, we'll summarize. Okay?

Dr. Everett, did you want to start? No?

DR. EVERETT: Yes. I am happy to kick things off. Brendan Everett. I think that, as some in the committee have said, we commend the sponsor for taking a medication for a rare disease and putting it through a clinical testing program to try and get it to market.

I think, unfortunately, in my opinion, we don't know what we're approving here. The benefit
is triglyceride reduction, but we're being asked to
approve a dosing frequency and dose that has not
actually been tested in a randomized controlled
way.

So I think there's clear evidence that the
drug is effective at lowering triglycerides at the
doses tested. It's not clear to me that, that
would be the case or at least that the same
reduction would be apparent with a different dose
and a different frequency.

So I have some concerns with basically
approving a dose and a frequency that has not
really adequately been tested at all in my view.

DR. WILSON: Others? Yes, Dr. Newman?

DR. NEWMAN: I just wanted to say that I
agree with all of that. This dose, the dosing
regimen has not been tested, so we really don't
know its effect on triglyceride.

DR. WILSON: Dr. Morrato?

DR. MORRATO: Yes, Elaine Morrato. I'll
comment on the secondary endpoints. I was very
disappointed to see not just a statistical effect,
because of obviously its small sample size, but not even directional clinical meaningful effects on pain, on the quality of life, and didn't seem to compliment where they were trying to go, and I would acknowledge that FDA's encouragement in this kind of situation where you're really trying to weigh benefit-risk.

Having that kind of information would be very useful at this point. So it's not just a lack of small sample, but just not even a directional effect.

DR. WILSON: Dr. Kane?

DR. KANE: With regard to this first question, one of the things that troubles me is that, in trying to interpret efficacy, there were 33 patients enrolled in the pivotal trial who received the drug. At the end of -- and this is intended, I believe, to be a chronic long-term therapy and, yet, at the end of one year, only 14 had completed and only 6 were on the original weekly schedule.

To me, that leaves a big gap between what
we're aspiring to and what we have evidence for.

Thank you.

DR. WILSON: Dr. Shamburek?

DR. SHAMBUREK: I agree with the discussion, but I think we also have to focus that this is an orphan disorder. We have limited patients. They are relying upon some of their phase 2 trial, where they did get a dose response, they did get a very impressive 77 percent reduction in triglyceride in their group in the original phase.

When they went to the additional extension trial, they saw a similar one, so putting everything else aside, I think they very well met in an orphan disorder with a very unmet need, that they achieved that compared to other studies.

DR. WILSON: Dr. Low Wang, did you have a comment?

DR. LOW WANG: Yes. I was very impressed with the degree of triglyceride lowering that was seen compared to placebo at month 3 with volanesorsen.

I think what I'm concerned about is the
percentage of patients who can actually tolerate the treatment and sustain it. So it's a small fraction, maybe a third of patients are able to continue through the entire year. And so I think that that's a concern. I think selection of patients is incredibly important.

For the patients who can tolerate this treatment, it could be life changing, but I think being able to find those patients is going to be key. But I don't think that, at the currently proposed dosing strategy, we really don't have enough adequate evidence for the specific dosing that's proposed.

DR. WILSON: So what we're going to do; we're trying to stay on track and we're trying to create major elements for our summary for discussion. And mind you, this is just 1A and we have several things to go through.

What we're going to do is, I'm going to summarize where we are at this point and then I'm going to go through all of these. And then I will then allow the sponsor, if there's any special
clarifications, once we've gotten through 1A through E. Okay? So why don't we do that? Can we do that?

I think that's acceptable to all. Yes. And any other further comments? Otherwise, what I'd like to do is to summarize 1A. I'd like to get beyond 1A because we have a lot to discuss and these topics are going to come back. Some of them, we've already gotten into 1B a little bit.

So in summary, panel members felt that we are being asked to critically evaluate and move forward on a medication design and a REMS program, et cetera that is not actually what has happened in the trials to date. Now, this point was made initially by Dr. Everett and it was corroborated by Dr. Newman.

We also had some concerns about the secondary endpoints and some of the other endpoints which were not powered to fully evaluate. Dr Kane mentioned that we had a considerable amount of dropout in the 66 patients in the key pivotal trial, especially after month 3. Dr. Low Wang made
the point that, especially at month 3, we had an
impressive triglyceride favorable effect for active
treatment.

So let's move on to B. How does the extent
of drug discontinuation after month 3 affect your
assessment of the efficacy of volanesorsen if at
all? Dr. Neaton?

DR. NEATON: I'll try. So I thought the
analysis that was done by the FDA, the method
imputation there was the appropriate one. It's the
one I would have done.

The sponsor attempted to collect the data
following drug discontinuation. I know that's
hard, but they collected it for 50 percent of the
people. It looks to me, at the dose that they
studied in the trial, there's a beneficial effect,
that it continues through 12 months.

I share the same concern actually that
Dr. Kane has. A sponsor said 19 people completed
the study. 14 of the 19 went on into the open
label and 5 of those had continued in the first 6
months, so they're kind of left with 9 out of 33
people.

So this doesn't appear to be the case that this is a drug that people will really want and will give up anything to take, is hard to make from these data in my mind. That relates, however, in my opinion, to the target population.

But in terms of the triglyceride effect, I think it's fairly robust.

DR. WILSON: Any further comments on that? Some of these issues, we're going to keep coming back to, so I'm going to summarize what you just said real quickly, Dr. Neaton, perhaps in almost as many words.

He was concerned about the study benefit. There was a study benefit at 12 months, but especially there's considerable drop-off after 3 months. And then what is the target population for this molecule in the future?

So let's move to letter C. Discuss whether the available data provide evidence that volanesorsen reduces the risk of acute pancreatitis. Yes, Dr. Epstein?
DR. EPSTEIN: Yes. It seems like the population that was studied was different than the population that we heard over here because of the low rate of pancreatitis and I don't think we can make that correlative judgment based on this data.

DR. WILSON: Dr. Burman?

DR. BURMAN: Thank you. I agree the data are certainly insufficient to definitively say that the drug reduces the risk of acute pancreatitis, but I would point out as a clinician and a researcher that elevated triglycerides do cause pancreatitis and that, if triglycerides are lowered significantly, that risk of pancreatitis is going to be less.

DR. WILSON: Yes, go ahead. Yes, Ms. McCullough [sic]?

MS. MCCOLLISTER-SLIPP: Looking at this as somebody from the consumer perspective, I mean, I don't have this condition, but if I were trying to decide based on what we've heard about the disease itself, if I were making a risk assessment, risk-benefit decision, I would take the odds of avoiding
pancreatitis by taking the drug.

I mean, it's potentially deadly. There is a drop in pancreatitis. The numbers aren't very big, so it's not powered the way that we would love for it to be powered. But there does seem to be substantial clinical benefit at least for some people. We don't know exactly who those people are because the numbers are so small. But I think the benefit is substantial enough that the choice should be available.

DR. WILSON: So I'd like to get a comment from our other hepatologists, GI experts. Could you weigh in on this and help us out? Do you agree with Dr. Epstein's assessment at this point, putting you on the spot, sir?

DR. RAUFMAN: Jean-Pierre Raufman. Evidence is always a hard word. I'm not convinced that we've seen evidence that the drug reduces the risk of acute pancreatitis, but I can infer based on the reduction in triglyceride levels that, if the study were powered more strongly and there were more people that we heard from in the open session, that
we would likely have seen a signal.

So I know I'm not giving a very strong answer here, so no. There's no evidence. At least evidence hasn't been provided, but I believe that, based on what I've seen, it is likely to reduce the incidence of acute pancreatitis.

DR. WILSON: Thank you. Dr. Everett?

DR. EVERETT: Just quickly, I think there's a good likelihood that this degree of triglyceride reduction could potentially lower the risk of pancreatitis. I don't think the data that we've seen support that, but I have a lot of sympathy for the numbers that you would have to enroll to see such an effect given the orphan disease status or the rareness of the condition that's being studied.

I do have some more concerns, though, with the actual ascertainment as an SAE ascertainment rather than a different kind of more routinized collection of these endpoints. You can potentially run into ascertainment bias and referral bias, especially when the clinicians who were caring for these patients are potentially unblinded just by
looking at their triglyceride curve over the past year or two.

That combines of course with the question that's next to it about dropout and so you have differential ascertainment on that basis, too. So you begin to worry that there is potentially a directional bias in terms of what kind of cases are ascertained versus not, just from a trial design perspective, even though I have some faith that, if you were to reduce triglycerides by 70 percent, you would have a reduction in pancreatitis in this population.

DR. WILSON: Dr. Neaton?

DR. NEATON: Just two comments; one, I think it's inconclusive, but the second, kind of following what Dr. Everett said, I would totally agree that basically it would have been better to collect it separately and ensure that people kind of understood that it was recorded through the entire duration of follow-up. I've been involved in too many studies where, even if the sponsor did what I think they said, they collected as a serious
adverse event and then adjudicated.

Investigators at the sites just have this mentality that, if you stop medication, it can't be a serious adverse event anymore. So there potentially is a reporting bias that differs according to whether people stayed on therapy or not.

So I don't know whether an intention-to-treat analysis is appropriate here or the on-treatment. I understood what the sponsor did was on treatment and what I understood the FDA was a better analysis on treatment.

I'd like to see and believe in an intent-to-treat analysis, but I'm not sure that we can. But in any event, it's inconclusive.

DR. WILSON: Dr. Morrato?

DR. MORRATO: My question or discussion point relates to maybe the generalizability of the study sample and maybe the external validity. So we heard from the sponsor that I think they were sizing the study, assuming 1 attack every 5 years based on a literature review.
The FDA slide looking at the results saw roughly 1 attack every 10 years and no difference in rates between placebo and volanesorsen. And that's different than obviously what we heard as the experiences of some folks in the open. So I'm trying to understand what's the general population for this and others may have a sense.

Is that rate of 1 every 5 years about right and so what we're seeing in the trial is a prototypical or a typical kind of patient? Or are we actually seeing a selection problem in which those that came in the trial really aren't representative of the clinical population.

DR. WILSON: Dr. Weber?

DR. WEBER: This is to follow up on Dr. Everett's comment about the bias to ascertainment. And if you've got 90 percent of the folks in the trial having skin reactions on, I think, the investigator's end, it was pointed out by Dr. Kane before. That's pretty much an indication, so that could have influenced the ascertainment of pancreatic events.
DR. WILSON: Ms. Cuaresma?

MS. CUARESMA: I'll take my doctor hat off for this to answer this, but I am here obviously as a patient representative and I feel as though I can kind of answer some of those questions because I've been there done that as well as the 13 people that spoke today.

Pancreatitis is happening way more than 1 time per year. And I can say that. I know at least 50 people, which is almost everyone with FCS right now, has been diagnosed jokingly that pancreatitis is very prevalent. It's happening a lot.

So maybe the data isn't shown here, but I can say that it is happening very frequently with people that have very high triglycerides. Most of the patients, including my own family, are over 2,000 on a regular basis.

So if we're looking at just reducing triglycerides in hopes that, that will help these pancreatitis attacks or other type of FCS-related issues, I think that the goal has been met. If
we're reducing triglycerides by over 77 percent with the medication, at least we're attempting to reduce the amount of pancreatitis.

DR. WILSON: Can we summarize? Can we move on? So I'm going to try to summarize. Our liver and GI specialists reminded us that we had relatively lower rates and the triglyceride lowering, we would expect to infer should work and larger outside of this current experience and moving forward with more trials and more patients.

We had several concerns by our epidemiology clinical colleagues and patient representative colleagues concerning bias, concerning blinding for the administration and/or the lateness of the serum, some concern about their inconclusive results for some of these findings, a selection bias potentially for participants in the trial. Perhaps they were healthier or once they especially were included within the trial, they perhaps assumed healthier lifestyles.

That's why we may have seen lower experience rates for not the primary outcome, which is
triglyceride change, but for the key clinical outcome, which was pancreatitis occurrence.

I apologize for that. There's a lot to summary, a lot of different comments. Any amendments, recommendations? You'll get your chances as we move forward here. We're only to part C. 1D, discuss whether the available data provide evidence that volanesorsen reduces abdominal pain.

So this is now abdominal pain in patients with FCS. Let's put our GI experts on the spot. We want to hear from each of them whether they think that it may reduce abdominal pain. Any comment on that, Dr. Epstein, no, on whether the evidence is sound that this reduces abdominal pain?

DR. EPSTEIN: I didn't the evidence was sound.

DR. RAUFMAN: Jean-Pierre Raufman. I agree that the evidence wasn't overwhelming and I'm not quite sure what the abdominal pain is caused by. I know that pancreatitis causes abdominal pain, but I don't know whether we're talking about non-
pancreatitis pain and, if so, what's the genesis of that.

DR. WILSON: Dr. Yanovski?

DR. YANOFSKI: Sure. Can I bring in quality of life, too, to this? Because I don't see it addressed separately. So I kind of feel a disconnect here because, on the one hand, this is a drug that's obviously difficult to take. Right? A lot of patients didn't tolerate it or had adverse effects.

When we heard our speakers, they almost uniformly -- and this is the same population because these were people who were on the drug who said, "I feel better. I had so many episodes of pancreatitis. I had so much abdominal pain. I have so much more energy." But when we actually try and look at the data in the blinded trial, we just don't get that evidence.

I was struck by the fact that about half of people didn't even report significant abdominal pain prior to the study, and that so few reported abdominal pain during the study, and that there was
no difference, and that there was also no measured difference in quality of life.

So given that there's serious adverse effects and it's a really difficult medication to tolerate, I would really like to see some evidence that patients feel or function better on the drug.

DR. WILSON: Yes. Just Ms. Cuaresma is next.

MS. CUARESMA: Yes. I actually had written that same thing down. When you look at the slides CS6, the full analysis study and then the quality of life, the weighted sum seems insignificant. However, I'd like to point out that we heard it firsthand here, so I don't know where the discrepancy is or why it's so different, but these are the people on the drug, and they're reporting that they are feeling better, and that their abdominal pain has lessened, and that their quality of life is better.

So I agree there was kind of a disconnect in some of the slides in some of the information that was given, but I just want to make sure you've
heard it firsthand here that it is helping the patients that are taking it.

DR. WILSON: Dr. Weber?

DR. WEBER: Part of the explanation is that we saw a biased sample. There were 33 subjects in the study and I think we heard from 6 today, so we may have had their positive effects as opposed to neutral effects.

DR. WILSON: Who is next? Dr. Morrato and then McCollister? Dr. Morrato?

DR. MORRATO: I'd just like to underscore that. I was going to make that same comment. I think we have to also remember that three-quarters of the patients withdrew from the study, so they obviously also had their experiences that didn't get to be voiced here.

DR. WILSON: Ms. McCollister?

MS. MCCOLLISTER-SLIPP: I found that the evidence of decreasing abdominal pain to be pretty much non-existent, but I think the company spoke to this. And I don't know the specific measures or questionnaires that were referenced. I'm not
familiar with them, but I'm familiar with 
questionnaires used in other conditions for studies 
that I have been involved in and most of them are 
not particularly good.

So I think we need to be aware of the fact 
that, just because these particular instruments or 
patient-reported outcome questionnaires didn't 
measure something doesn't necessarily mean that 
there isn't a reduction. And I completely agree, 
you don't fly across the country to go on FDA 
advisory committee and just say that the drug is 
not good.

Generally, it creates a bias of bringing 
people in. You get excited about something that 
benefits your life, but I do think that we need to 
acknowledge and the company has acknowledge that 
these particular instruments may not be sensitive 
or may not be tuned with the specific types of 
abdominal pain that might be present in this 
population.

DR. WILSON: Dr. Newman?

DR. NEWMAN: I just wanted to mention that
abdominal pain is very subjective and the only way to evaluate that is in a placebo-controlled trial. And that may explain some of the differences we see in these data compared to what other people spoke about today.

I didn't think there was an effect on abdominal pain in this particular study.

DR. WILSON: Dr. Neaton?

DR. NEATON: I just was going to bring it up earlier, but since we're talking about quality of life, the sponsor did this trial largely outside the United States. And they said they're working on a quality control, quality of life instrument that's more suitable for this population, but in studies that I've done internationally, you have to be very conscious of the culture that you're even giving the questionnaire in.

So I don't know to what extent the large population outside the United States may have had some impact on his findings.

DR. WILSON: Dr. Low Wang?

DR. LOW WANG: So one of the other comments
I wanted to make is that I didn't expect to see a difference in the questionnaires because I think that the sensitivity is very low with such a small population.

So I would have been extremely surprised if there had been a difference between the populations in terms of quality of life as measured by these questionnaires.

So given that, I think that the available data don't provide evidence that volanesorsen reduces abdominal pain in these patients, but if I could move on to E, I do have to say again that I think that, in terms of the magnitude of triglyceride lowering in the patients who can tolerate, and can stay on the treatment, and can sustain this, that degree of triglyceride lowering of 90 some percent compared to placebo is expected or has the potential to improve their quality of life and reduce their risk of pancreatitis.

So I do think that, in terms of overall magnitude of clinical benefit for the patients, the right patients, so I think selection of the right
patient population is incredibly important. It could be of benefit and I think that's a key point for an orphan drug.

DR. WILSON: So I'm going to try to summarize this rather rapidly because some of these issues are going to come up again. We started out with a very simple question, whether this reduced abdominal pain, and our GI experts especially said the data were not convincing that it did reduce.

Then we had an add-in, what about the quality of life, and we spent most of this time discussing quality of life. And we had a variety of interpretations, including a difficulty assigning what is a quality of life in different cultures and different populations.

I think also concern about the quality of life types of questionnaires. Instruments are difficult to assess in the population sizes that were studied here.

So let's move on to the next E point. I believe that's our last one for this. Considering both the benefits that you expect based on the
magnitude of triglyceride lowering as well as what was observed in the development program, how would you characterize the overall magnitude of clinical benefit that results from treatment with volanesorsen?

This is sort of putting it all together. Here, most of this is a summary for this question. Dr. Shamburek?

DR. SHAMBUREK: I waited for this question just to summarize the pancreatitis, the abdominal. I think the real key in familial chylomicron syndrome is getting the triglyceride under 1,000. Volanesorsen reduced the triglyceride 77 percent, but I think more importantly, the triglyceride went from 2,267 to 590. That's a magical number.

People who have followed these patients' natural history and those who could tolerate diet and who were under 1,000 did well. So I think, at the beginning, I was absolutely convinced that there would be a favorable impact on clinical manifestations based on the natural history.

However, the study itself, the CS6 pivotal,
I am not convinced showed that. And I think some of that, we've heard of the powering and design.

The patients were 46. The patients that we heard start young and have repeated bouts. Some of those go on to chronic pancreatitis. Some of them get the endocrine, exocrine.

The older group is -- in one sense, if we're saying one episode every 5 years is a lower-risk population, not that it's not significant.

If we had a higher risk one, we've heard on the internet people coming in, several people having 30, 50 episodes of pancreatitis. We almost need, like with smoking with pack-years, a pancreatic score where you've had several.

Had there been either one of two things, one where you had people who are out there -- and I think it's part of the group with multiple relapsing -- we would have seen it in a 1- or 2-year study.

Otherwise, this other one that's getting 1 in 5, there's no way in a 1-year study you could. So I personally think the study did not show that,
but I think the drug should, based on epidemiology -- and again, we don't have the evidence -- would end up helping abdominal pain and pancreatitis, but there's that population limitation.

DR. WILSON: Dr. Newman?

DR. NEWMAN: I'm not sure some of what was just said, but I do think that the drug lowered triglycerides and that it will do so with another dosing regimen that hasn't been studied yet. And I think that will confer a clinical benefit on the patients that have familial chylomicronemia syndrome.

So even though this clinical benefit was not demonstrated in this phase 3 program, I believe that there will be a benefit because of the significant triglyceride reduction.

DR. WILSON: Yes, Dr. Epstein?

DR. EPSTEIN: It's incumbent upon the sponsor when they first design the study and 90 percent of the problems occur in the original design. And there was inclusion issues here.
There was study design issues throughout. There were flaws in the study. And part of that's because of the small orphan drug. It's very hard.

But that was a flaw and they didn't get the right population, which I think everyone here has said. So we look at two things, safety and efficacy. And here, they demonstrated only the reduction in the level of triglycerides at 3 months. They did not demonstrate the efficacy to treat the patients like we heard that's missing.

DR. WILSON: Yes, Reshma. Go ahead. And say your full name. I apologize. I'm good with your first --

DR. KEWALRAMANI: No problem. Reshma Kewalramani. I just want to put a fine point on the fact that, as designed, the study was powered for a decrease in triglycerides at the 12-week time point.

As such, which is what's on page 59, I didn't have an expectation that, in this small number of patients, we would be able to see beyond triglycerides because the numbers are small and it
is powered for triglycerides.

   The fine point I want to put on that is
simply that the study was overwhelming positive on
the primary endpoint as it was described to be.

   DR. WILSON: Any further discussion?

   DR. KANE: Yes.

   DR. WILSON: Yes. Dr. Kane?

   DR. KANE: Kane. Just to carry this
forward, then, we're asked to comment on the
clinical benefit as demonstrated in the information
that we have on hand and the primary endpoint is 12
weeks of triglyceride reduction.

   No one is disagreeing with that, but I think
everything beyond that is a bit of a leap of faith.
Thank you.

   DR. WILSON: Dr. Morrato?

   DR. MORRATO: Yes. Just to get back to
Dr. Epstein's point, I was struck by the
repeatedness of the FDA's advice to the sponsors to
be addressing the design issues of these other
secondary endpoints, knowing in light of the full
benefit, efficacy benefit-risk profile. So I would
agree that it met its primary, but I also think it's the study and the sponsor fell short of meeting the FDA's suggestions to be addressing this when they had their post-phase 2 meeting.

DR. WILSON: I'll try to summarize. You get your chances to edit whatever I say here. So Dr. Shamburek started this section off here. The key was that the triglyceride lowering was really quite remarkable for patients who were enrolled and especially given their age.

They've survived to a greater age than many of the patients we expect to have this and who might have more severe symptom and more severe triglyceride problems at a younger age.

Almost every person who spoke to this felt that we could infer clinical benefit, but we have not observed that. The emphasis was especially placed on the 3-month result rather than what happened starting 6 months, 9 months, 12 months when there were trial modifications, which kept our confidence up for inference, but we do not have solid proof to put our fingers on the data to say
that there's definite benefits because of various changes.

Why don't I leave it at that? Any further edits? We're ready for question 2. So I've been informed from the sponsor if anybody from our committee needs any specific clarifications, we can turn to the sponsor at this point, but the sponsor's really generally not part of -- is there anything that we've misstated?

The sponsor's asking for the floor, but other than that, only a clarification, I believe at this point, because you're not part of the discussion.

DR. O'DEA: Understood. So the clarification is around the dosing regimen. I just wanted to point out that, that is the dosing regimen that was used in the CS6, continues to be used in CS7.

We have about 60 patients who have been treated with this dosing regimen and the only addition now is to add a weight-based dosing element to that paradigm. So it's the established
paradigm that we've been using throughout.

The other thing is, there was a comment about three-quarters of the patients dropped out, 60 percent of the patients completed, and currently in the continuing long-term trial, 80 percent of the patients are retained.

DR. WILSON: Thank you very much. So we'll move on to question 2. Aside from thrombocytopenia, discuss the tolerability and safety of volanesorsen such as injection site reactions, immunogenicity, hypersensitivity, liver-related safety, renal-related safety, and any other safety concerns.

But to hold off on thrombocytopenia as I understand, we're not going to remember that, so we're not going to talk about platelets. So let's first hear about any reactions concerned about those first ones, injection site. Dr Newman?

DR. NEWMAN: I think we all saw that that there were injection site reactions in the patients who were allocated volanesorsen. These included discoloration of the skin, erythema in duration,
pain, and itching

    They did not always resolve. And also there were some hypersensitivity reactions and I will wait to discuss liver and renal.

LX Thank you. Dr. Epstein?

    DR. EPSTEIN: Yes. Having reviewed trials of biologics and other injectables, these are high rates. These are way above what I've seen with any other trial.

    DR. WILSON: So your concern is that the percentage of injection site reactions is greater than you might expect from other biologics that would be used to treat, for instance, gastrointestinal diseases.

    DR. EPSTEIN: They typically hover around 5 to 8 percent. Here, we have 87 percent.

    DR. WILSON: Dr. Budnitz?

    DR. BUDNITZ: Dan Budnitz. I agree with the comments about injection site reactions, but in terms of understanding the safety of these other adverse events; immunogenicity, hypersensitivity, liver, and renal, I think just our safety database
is just so small it's hard to say much of anything
with under 100 patients with a high dropout rate,
but that's where we are. So we'd need more of a
safety dataset.

DR. WILSON: Dr. Burman?

DR. BURMAN: Thank you. I'm just also
concerned about the presence of antibodies and what
role they may play in abrogation of the effect or
any other immunologic response.

DR. WILSON: To follow up on that,
Dr. Burman, your concern about the antidrug
antibodies and what that might mean over time; is
that where that's going?

DR. BURMAN: Yes. Thank you.

DR. WILSON: What would you want to see in
the future, for instance?

DR. BURMAN: Definite measurement of
antibody with their titer and then nice detail
correlation with benefit for the drug, to make sure
it's not abrogating the effect.

DR. WILSON: So you've already moved a
little bit into the immunogenicity, but that may be
related to injection sites as well. So to follow up on what Dr. Burman's already getting us into, immunogenicity, any specific questions there or comments, I mean, or understanding of where we are? Is there concern about the antibody titer development? Dr. Epstein?

DR. EPSTEIN: So with antibody titer, it's very important to fully understand because, for us, with the biologics, for decades, we did not know what was going on with the antibodies. And we later determined they cause secondary loss of response to the drug.

So e would have people dropping off because the antibodies were building up early. We weren't using the proper dose.

So you need to do therapeutic drug monitoring, which is your antibody levels, your drug levels early, early, sort of in the induction, if you will, and determine whether or not you have an antibody former or not. And those patients require dose adjustments.

They require sometimes secondary medications
and they can also be at risk for other adverse events, hypersensitivity reactions, antibody reactions, flu-like symptoms, immunogenicity, and even anaphylaxis.

DR. WILSON: To follow up on some of these immunogenicity issues, have we seen enough over even 1 year for pause and restart? The sponsor did show information on that. We don't have much data beyond 1 year. These trials are largely short term as opposed to 3- or 4-year types of safety data for antibody development, so that's another comment to build on Dr. Epstein's.

Yes, Dr. Kane?

DR. KANE: Kane. In my experience with this, this frequency of antidrug antibody is not that unusual. I'm not particularly troubled by this event. Neutralizing antibody would be a different story or if we had a closer implication of a particular subgroup of antibodies to the thrombocytopenia, that might be a different story. That's not the case here, from what I can see.

Thank you.
DR. WILSON: Let's move on to hypersensitivity. Any comments on hypersensitivity? None specific? Dr. Epstein, did you want to make a comment on it, you think?

DR. EPSTEIN: Just that anaphylactic rates should be about 0.1 percent, so should these patients be carrying an EpiPen? Obviously, this patient had to have epinephrine. They're at home. Where are they getting it? Who is injecting them? Anaphylaxis is very, very serious.

There is going to be a rate with any injectable, that's true, but it should be quite low. We don't know those numbers. And also, we have somebody with serum sickness, which is a very damn serious disease, a very life-threatening disease, and so we have now two of these in a small number of patients. But we don't know what that means.

DR. WILSON: So I'll cut to that in a summary, but you can guess it's going to be we need more information. But for instance, I don't know what to say. I don't think any of us know when we
have only one of each sort of is a major problem.

Liver-related safety? Our hepatologists, yes?

DR. RAUFMAN: I don't think there was a signal for liver or kidney. I didn't hear anything significant.

DR. WILSON: Dr. Epstein concurs, I believe. And renal-related safety? Dr. Low Wang?

DR. LOW WANG: So I was surprised at the degree, at the number of renal events, the renal adverse events in the volanesorsen-treated patients compared to placebo. So on both the worsening proteinuria, the worsening creatinine, the overall rates were a lot higher, so that was concerning, albeit the numbers were small.

DR. WILSON: Any other safety concerns?

(No response.)

DR. WILSON: Ms. Sinclair, I'm sorry. I apologize.

DR. SINCLAIR: Hi, Susan Sinclair. I think that I won't speak to the specific signals and whether I think they're important or not, but I do
think, like is previously stated, that the safety
database is too small.

However, there are data being collected
right now in the open-label extension that could
inform this. It'd be helpful to get a look at
that. Also, when I think about the quality of
life, I think about patients who, initially, are
coming to terms with, maybe I don't have to worry
about pancreatitis so much now, so it takes a while
to maybe come to terms with that.

Maybe that's not reflected immediately in a
quality of life instrument. However, if there's
flu-like symptoms, fatigue, and maybe inconvenience
going in for blood draws and traveling to a site,
that could maybe offset some of the quality of life
improvements that you would hope to see.

Also, those instruments, though, are well
validated in multiple languages across the world,
but then again, the sample size is small.

DR. WILSON: I'm going to summarize this.
There is concern about injection site reactions
were greater in the active treatment arm with
volanesorsen versus the placebo. And it was not just a mild increase. It was a rather large increase in comparison to others that have been used for biologic injectables.

There was less concern about the immunogenicity, specifically the antidrug antibodies. There was definitely some concern because, although rare, there have been some hypersensitivity reactions, especially with at least 1 case of anaphylaxis and 1 of serum sickness.

There was no real concern for liver-related safety. There is some signal for renal-related safety on the other hand and that perhaps should be paid a little bit greater attention moving forward. And no other specific safety concerns were brought up.

So at this point, it is five minutes to 4:00. You're going to get a five-minute break basically to have a biologic break. And please come back so that we can finish up on time. Thank you.
Whereupon, at 3:55 p.m., a recess was taken.

DR. WILSON: We're going to try and get going in a couple of minutes, so let's please take your seats. Okay. Please take your seats and the start of this. We're now up to question 3 and I'll tell you what's going to happen between now and our target is to end at 5:00.

We're going to have question 3, question 5, and question 7. Question 4 will be visited as part of the vote and, if we have time after question 7, we will come back to pediatric issues with question 6. So we're going to move on to question 3, so if we could pull that up.

So discuss the risk for thrombocytopenia and bleeding associated with volanesorsen. And A is, discuss your level of concern for the risk of thrombocytopenia and bleeding with chronic treatment with volanesorsen. I'll stop there.

Let's do A first.

Open for discussion. Yes, Dr. Ortel?

DR. ORTEL: So if I can lead off, Tom Ortel,
the way that I just approach part A, which is not
the monitoring or the parts B and C, just when you
talk about level of concern, I'm looking at the
thrombocytopenia from the perspective of the way
that Dr. Roberts described it, that there's two
types.

There's this slow type that seems to be
something that, if you're monitoring, you should be
able to catch, you should be able to intervene. So
I'm not really worried about that. That is
something that you can catch.

The second one, though, is a little bit more
concerning, the one where it can precipitously
drop. The only thing that I would say about that
is that, really, a monitoring system -- it's very
difficult to catch that because, as some people
mentioned, that's an idiosyncratic event. You
don't know when it's going to happen.

But looking at the numbers that were
provided of the 8 patients that had the severe
thrombocytopenia, 4 of them were in the 40,000
range, which is not a number I would even treat
necessarily. So I'm not as concerned about that, but these people are not dropping severely low.

Only one of them dropped below 10, which is again where I put my marker for what I would be concerned about, spontaneous bleeding. That's the thrombocytopenia part.

The bleeding part is interesting because I think it's divorced from the platelet count. It isn't that there's a clear relationship between a platelet count and the bleeding manifestations, suggesting that there might be something else also going on here, either with some qualitative platelet defect or some other kind of thing that's separate, but fortunately, we didn't get a lot of bleeding symptoms that were fatal bleeding outcomes or major bleeding outcomes, so I think that you have to look at that separately.

So if I look at them all separately, I'm not as concerned about it as it was initially put together.

DR. WILSON: Dr. Stroncek, over here?

DR. STRONCEK: Yes. Hi. This is Dave
Stroncek. I agree that this type 1 thrombocytopenia is not as much of a concern because it can be picked up and it's slow. I do have a concern about the type 2 thrombocytopenia. It looks like it will happen.

Even anything below 50,000 people do have prolonged bleeding time. So I think, if you give this drug to enough people long enough, someone will have a serious bleed. And I don't see any way to eliminate that risk with this drug.

DR. WILSON: Dr. Kane?

DR. KANE: I share a lot of the same expressions we just heard here and I also focus on the severe precipitous thrombocytopenia. Fortunately, there's been no clinically important bleeding in a carefully constructed and conduct a clinical trial.

I think it's one or two orders of magnitude different in the population, even including a REMS because we don't really know that the REMS is going to achieve what we hope it will. The devil's often in the details.
So to me, the 8 patients in total with FCS developed the below 50,000. And in the two most direct clinical trials, CS6, CS7. There are 6 out of 76 patients below 50,000. I think, to me, that's a high risk. Thank you.

DR. WILSON: As a non-hematologist, what about the threshold that have been used for the studies up to now? Dr. Ortel's especially not so concerned with a 10 to 30, but there's been a lot of highlighting in the write-ups that we've seen for lower numbers and also whether thresholds at which time the medications were given or not given. Could you help us?

Before we get to a voting question, this would later potentially relate to that. But what do you think of the thresholds that have been used in the development program up to now?

DR. KANE: If I could continue on, then, I think the thresholds that you're looking at are defined mostly by the adverse events reporting system. Below 50,000 is considered to be severe. And to me, that's where the concern really rises.
I think also, in a more general population, there are going to be other conditions, drugs, diseases, co-morbidities adding to the risk for thrombocytopenia. Also, there's not a close good correlation that I know of between a particular platelet count on a particular day and the actual risk that, that individual is going to bleed, so I think we've got a loose correlation, but simply more or less a warning sign her.

The other point I would say; the bruising, the epistaxis, the gingival bleeding probably, compared to the importance of this treatment, are not that important in and of themselves. Thank you.

DR. WILSON: Dr. Shamburek?

DR. SHAMBUREK: Yes. I'm not going to repeat anything. The bleeding thing worries me a little bit because of the unpredictability and then we had our experts talk about the platelet. But I think my most feared complication in these patients is necrotizing hemorrhagic pancreatitis.

If volanesorsen prevents it and we don't
have it, that's good, but patients who develop this
and end up having very low platelets might not have
very good outcomes. So I mean, that's just
something to think about. We haven't seen that,
but that's where the platelet or bleeding problem
could become an issue in the treated patients.

DR. WILSON: Dr. Ortel?

DR. ORTEL: Tom Ortel. Also following up on
some of the things Dr. Kane mentioned, I agree
that, when you put this drug out in the real world
and people are using it. When I'm talking about
platelet counts and where I get concerned about it,
it's in the patient who hasn't got anything else on
board. It's just platelet count and looking at the
platelet count and where it goes.

When you put a situation where the patient
may also be taking an aspirin or they have
pancreatitis or they have something else, then the
numbers become more important as far as once you
drop below that 50. So using it as a target is
reasonable.

DR. WILSON: Yes, Dr. Epstein?
DR. EPSTEIN: From a hematologic standpoint, it's true that 10,000 or below is when you get spontaneous oozing of blood from all of the mucosa in the body. But at 50,000 is when you see patients that might take an aspirin or Naprosyn or they're on Plavix or another antiplatelet drug or an anticoagulant, coumadin, or what have you.

That's where you get massive GI hemorrhages and we have enough trouble because we get called and I know this data is not in this study, but this is real world. We get called every night for these bleeds, maybe 2 or 3 times a night for GI bleeds, and it's always the same story. And if they have a platelet count below 50, we're not going to be able to stop that bleeding with our hemostatic methods.

So that's a real concern. And I didn't see in the REMS and I was looking for this, that they controlled for aspirin, and non-steroidals, and anticoagulants, and for antiplatelet drugs.

DR. WILSON: Can we try to summarize this at this point? We started off discussing this issue, 3A, with Dr. Ortel's comments. He favored the
approach with the type 1, which he thought is
somewhat trackable and intervenable.

Type 2 for low platelet count is
idiosyncratic and a concern. He has a little bit
less concern clinically if there is less. The
greater concern is that the platelet count is less
than 10,000, but agreed with the monitoring systems
in place, especially to raise flags when 50,000 is
reached, but there seems to be some element of a
gray area between 10,000 and 50,000.

All of the commenters made the point that
there seems to be a disconnect between bleeding
episodes and individuals' specific platelet count.
And there was a wish for greater information on co-
morbid conditions and medications or conditions
that may especially affect platelet count or
platelet function and other hematologic function as
we move forward to a wider use of this medication
and especially what would happen for individuals
taking antiplatelet drugs or drugs that affect
platelet numbers or function.

So that's most of what I had. Any comments,
extra edits?

(No response.)

DR. WILSON: No. All right. So let's go on to part B. The applicant has proposed labeling that recommends intensive platelet monitoring. I'm sorry. I'm going to have to read this on my copy, not on the screen because it runs off, such as a minimum of every two weeks for the duration of treatment with this potentially lifelong therapy.

Discuss whether the proposed frequency of monitoring adequately addresses the risk of thrombocytopenia and bleeding as well as whether such monitoring would be feasible in clinical practice. If you disagree with the proposed monitoring scheme, discuss how patients treated with volanesorsen should be monitored for thrombocytopenia or bleeding if approved.

Dr. Ortel?

DR. ORTEL: Tom Ortel. I think that some monitoring plan is appropriate for this type of drug as far as monitoring platelet counts. I think monitoring every two weeks might be more than you
need for this slow drop. I think monitoring every two weeks is not necessarily going to pick up an idiosyncratic reaction.

It's hard to say what's the sweet spot for what would be the right frequency with which you want to be checking the platelet count on these because those two are completely different things, but you do need some kind of monitoring in place while the patient's taking the drug.

DR. WILSON: Dr. Everett?

DR. EVERETT: Yes. I want to echo Dr. Ortel's comments. I also want to say that measuring something every two weeks within the context of a highly structured, very focused clinical trial is very challenging. It's much more challenging to do on a routinized and reliable basis in general clinical practice.

So I think that, even if you proposed to check platelets every two weeks, the reality is that it might happen for a couple of the patients on these medications, but the vast majority are not going to be able to have that rigorous platelet
ascertained.

It's going to be a challenge. If you think it's important to evaluate platelets every 2 to 3 weeks, it's going to be difficult to actually maintain that frequency of platelet ascertainment in general clinical practice.

I share Dr. Ortel's concern that it doesn't seem to prevent the possibility of a precipitous drop in the clinical consequences thereof as well. I do think it's necessary to have such a plan, have.

DR. WILSON: Dr. Budnitz?

DR. BUDNITZ: Dan Budnitz. I agree with the comments before. Just in my mind, the two-week monitoring isn't so much to prevent the precipitous drop, but to limit the amount of time that a patient is hanging out at less than 10,000 platelets. So I see the point that every two weeks might not be as clinically feasible, but you don't want those patients hanging out for 8 weeks when they have intercurrent medications added to their regimen and other things going on.
Just we wonder if either the FDA or the sponsor might have a recommendation on when this two-week testing happened. Does it happen 48 hours before the next dose? Does it happen 48 hours after the next dose? I don't quite know the mechanism of action and when an appropriate time would be, but maybe if there could be such a recommendation, that would be helpful to folks.

DR. WILSON: Any further comments? Yes.

MS. McCOLLISTER-SLIPP: Speaking from the perspective of the patient again, I don't have this particular condition, but I have others. I think every two weeks is going to be incredibly burdensome and very difficult.

My hunch is that, over time, as people get used to the medication and they've been on it for a while, they're going to be really irritated by the fact that they have to make it to the determine every two weeks to take this medication. I don't live with the disease. I don't know what the relative constraints are on the way you live currently.
So I think that's really important, to be able to let people to make that decision as opposed to somebody like me, but it might be the kind of thing where I know there are companies now that do in-home blood draws. That might be something that could be coupled with a REMS strategy if it really is that clinically important, to make sure people don't hang out at a low level of platelets.

I don't have the expertise to assess that importance, but I think, from a practical perspective, it's going to be really difficult to sustain over any period of time. And we don't have the data to, like, provide any long-term guidance about how long that needs to happen just because it's a small population, it's a new drug.

But I don't think it's all that feasible. I mean, I don't think it's realistic that that's going to happen on a regular basis.

DR. WILSON: Dr. Morrato?

DR. MORRATO: I would like to build on that and I think also you raised a question earlier as to how do you know if that's the dosing schedule
for the rest of the life of the drug, too. So there are examples of drugs like clozapine in which its regular counts.

Also, there was supposed to be regular liver function testing with statins, so there are other examples. And often, what happens? You get something in the label and it's used. And then you get data and, years later, you're changing it.

I think this would be a good case in which this is also enhanced pharmacovigilance, the way the sponsors have talked about it. And I would rather see some prospective discussion around what data, information would inform label changes.

So that's sort of prospectively built in, so as the pharmacovigilance is coming in, it can be more updated over time. So I know it's not uncommon that, if you've made it through a year at this thing, maybe we can make it down to four weeks and your year 2 and beyond, et cetera. And so build it into the design up front rather than saying this is it, forever.

DR. WILSON: Yes. So Dr. Morrato, thank
you. I wanted to build on her comment and there was a question back to our pharmacologist and hematologist. Is this concern about type 2 that much of an issue? For instance, if your platelet count is above 100,000 and you're going along 100 to 150,000, might you still be at risk for this severe drop?

Do you have any opinions, any of our hematologists or pharmacologists on that? Dr. Ortel?

DR. ORTEL: I didn't get the impression from the data presented that, if you started out a little bit lower, you were more likely to have a precipitous drop than if you started out a little bit higher.

That was from those figures that you showed. I don't think there was any correlation with where you started.

DR. WILSON: Yes, and we also only have a handful of cases for this as well, but thank you. I think that's going to be a question that's going to always come up. Any others? Yes, go ahead.
MS. CUARESMA: Sorry. Go ahead.

DR. WILSON: Dr. Ortel, go ahead and finish up, though.

DR. ORTEL: So just to follow up on the questions on monitoring and coming in and getting monitored, speaking from the standpoint of somebody who runs an anticoag clinic, patients do come in and get their INRs checked. If they don't come in, they don't get their meds. Patients with sickle cell have to come in and get their counts checked or they don't get their Hydrea or they don't get their pain meds.

I mean, there are ways that you can link not giving the patient a year's worth of medication and then tell them to come in every 2 to 4 weeks. So I think that there's ways that you can do it and patients complain about coming in to get their INR checked, I guarantee you, but they do it.

DR. WILSON: Thank you. Dr. Weber?

DR. WEBER: Just a question for the group, for the hematologists. It may reduce the burden of having to do this. Is there point-of-care testing
for platelets that would make it more simple or is that not widely available?

    DR. ORTEL: I don't think there's a point of care for platelet testing, but there's also nothing that says you probably won't see this occurring in your local pharmacy. They'll have the walk-in-and-get-your-platelet-count-checked.

    They're doing everything else in pharmacies. Amazon will probably do it soon.

    DR. WILSON: Ms. Cuaresma?

    MS. CUARESMA: So that actually was where I was going to go just as a patient perspective again, to go in every two weeks. We do that now and, just as what you said, if a patient is suffering, they'll go in every two weeks to get their medication.

    So maybe for some patients, but the majority I feel will make it in every two weeks for them to be able to get the medication.

    DR. WILSON: Can we summarize this at this point? So the question is related to how often to monitor. And most of the panel felt that two
weeks' interval is fine. And this is practicable, but is burdensome. And the question has been raised especially by our consumer advocates and experts at the science level is, couldn't we find ways to perhaps lengthen that interval for some individuals.

Then the question also comes up for how we might get better at detecting the people who are especially at risk for this type 2 drop in platelet count. And we're still vexed, I think. We're challenged for how to find a solution to identify those people before an event might occur.

The one last thing I think is that there is some tension about whether patients and providers can work together for two-week intervals. The hematologists remind us that this is common for warfarin dosing. Patients who are successful; it can be linked to the medication refill.

So let's move on to the next one, letter C. The applicant has proposed a dosing algorithm that recommends a dosing frequency based on platelet level and body weight. Discuss whether the
available data in the clinical development program are adequate to inform dosing recommendations for labeling and would ensure the safe use of volanesorsen.

Dr. Ortel?

DR. ORTEL: Tom Ortel. So I think that a dosing algorithm strategy makes sense conceptually. I think that the data that they've got to support what they're proposing is extremely limited, but again, it's very small numbers, but some kind of dosing adjustment is reasonable.

We do it for other medications where we're treating patients with thrombocytopenia or thrombocytosis. So that concept is there. The one thing that's not mentioned in here, but that I do have a significant problem with is the concept that the recommendation for a treatment is made with steroids.

I think that we need to educate the hematology community about the medication so that they know how to treat it, but to recommend a drug for a phenomenon that we don't even know why it's
occurring. We don't know that there's an immune-
mediated component to this. To recommend steroids, 
I think, is very dangerous.

DR. WILSON: To follow up on that, could you 
make a comment also about platelet replacement
since that's close to your heart as well, so under
which conditions my patients receive platelet 
transfusions.

DR. ORTEL: So platelet transfusions
definitely needs hematology input or otherwise what 
you really use platelet transfusions for is mainly 
for bleeding manifestations, not for just a number. 
So I would be cautious about recommending any kind 
of transfusion cutoffs for the number alone, but if 
the patient comes in bleeding, then platelets are a 
reasonable alternative to use.

DR. WILSON: Other comments? Dr. Stroncek?

DR. STRONCEK: Yes. To your point, I think 
it should be pointed out that the algorithms are 
reasonable based on the data, but the data is 
really very limited. And then I think the 
recommendations are good ones to make the drug as
safe as possible, but they really don't ensure the
safe use of the drug.

I mean, they minimize the risk, but they
don't ensure the safety.

DR. WILSON: Dr. Kane?

DR. KANE: I was going to say, I think that
the weight-based algorithm is applicable in the
overall population. Considering all the different
forms of thrombocytopenia, I was not confident that
it would in and of itself enable us to escape the
sporadic and severe thrombocytopenia.

DR. WILSON: Others? Dr. Morrato?

DR. MORRATO: My comment relates to how you
convert this into labeling and thinking about it
as, once it's in label, it becomes very set. And I
think that the available evidence is kind of scant.

I was compelled by the FDA's analysis that
countered the company's. And I'm sure there's a
lot more information that we'll learn once it's on
the market. So I don't know if there's an in-
between zone as opposed to saying this is the
dosing regimen in the label versus a guidance that
could be adaptive over time as things are learned. I'm not convinced the data we've been presented kind of meets that standard of labeled dosing.

DR. WILSON: Dr. Neaton, did you have a comment?

(No response.)

DR. WILSON: No. Anybody else?

(No response.)

DR. WILSON: So I'm going to summarize this. The question under discussion is dosing of volanesorsen and the patient's weight. Especially our pharmacologist and hematologist says that this makes sense, this is what is commonly used for other platelet disorders. And our hematology experts voiced concerns about steroid use for patients with low platelet counts, also about any transfusions for patients without bleeding, and for patients also I think the summary from them was as well individuals with low counts should have a hematology consult for the best advice on how to move forward.
Then it was reiterated that we can minimize risk, but we still have to translate this into safe practice. So we're ready to go, I think. Now, we have a comment, I think, from the FDA. Dr. LaCivita, is this the right time for you?

DR. LACIVITA: Yes, this would be.

DR. WILSON: Thank you.

DR. LACIVITA: So I'd like to pull up if it's okay sponsor slide CO-82. I don't have access. Okay. So the next question; I don't want to steal your thunder, but the next question is regarding the REMS and I just wanted to make sure that, for transparency, the advisory committee knew what they were voting on.

DR. WILSON: Could you have the mic a little closer so we can hear you a little better?

DR. LACIVITA: Sure. So I wanted to make sure that you understood that the REMS that is being presented by the FDA does not include adult patients confirmed of the diagnosis of FCS. It really includes prescriber certification, pharmacy certification.
The documentation of the safe-use condition would be the patient-provider agreement form, so they're informed of the risks before they start treatment. The monitoring is not a blood draw that's done before the patient gets the dose. It is a status form that we would follow up with every 90 days.

So I just wanted to make sure that point of clarification was clear and the things to the right, where the sponsors included the laboratory analysis, the patient blood draw are not part of the REMS. They are voluntary things proposed by the sponsor. Thank you.

DR. RAUFMAN: Can I ask a question?

DR. WILSON: Yes. Let's get this clear. This is an important issue. Yes, go ahead.

DR. RAUFMAN: Does it require that the patient have had an episode of pancreatitis?

DR. LaCIVITA: The proposal does not include that.

DR. WILSON: Yes. So Dr. Morrato, I want to spend a minute or two on this because we're going
to discuss it, but let's make sure we're clear on what we're discussing. Dr. Morrato?

DR. MORRATO: So two clarifying questions, because we had a question over here about, does this preclude pediatric use if they're not verified age or can you use it off label?

DR. LaCIVITA: The FDA's proposal really focuses on the risk and it does not at this point in time. But we'd like to hear the committee's thoughts on that.

DR. MORRATO: Then the second piece was, if I'm understanding, every 90 days, someone is giving FDA or this system a status. And in that status report would be their platelet count.

DR. LaCIVITA: Collecting information about their platelet count, maybe a bleed, things like that.

DR. MORRATO: So it could be 1 test in 90 days, not every --

DR. LaCIVITA: There could be multiple tests.

DR. MORRATO: Right. So what would happen
if we all agreed that every two weeks is the right thing to do and they are not doing that? What would the system feed back? You have one platelet count, so something's happening. So what would the REMS do in that situation?

DR. LaCIVITA: The status form would collect information with regard to a platelet nadir and maybe specific adverse events that were happening regarding that.

DR. MORRATO: So what's the feedback loop to the patient or the doctor as it relates to prescribing, anything or dispensing?

DR. LaCIVITA: Because the management of these patients is complex that will be under medical care.

DR. MORRATO: Then the last one is around informed consent up front. I think I heard that.

DR. LaCIVITA: Yes, so the patient understands the risks and they're aware of the need to have the monitoring performed.

DR. MORRATO: Yes. So since this is a lifelong drug, would there be a re-assenting kind
of process built in over time as there's new
information that comes out in a prospective way.
It's not like, I've been taking this for 10 years,
I'm going to really read this new med guide thing.

How do we help ensure patients are staying
up to date and re-attesting that it's still the
right thing for them?

DR. LaCIVITA: Those are considerations that
we could build into the REMS, but certainly your
thoughts on that would be helpful.

DR. WILSON: As a follow-up, would you like
us to discuss elements of some of these boxes,
these decision boxes, or no, just the general
concept, general concept?

(No response.)

DR. WILSON: So we're now going to go to
question 5, discussion point 5. We're skipping 4.
We may come back to that, but we're going to go 5
and then a voting question. And then we're also
skipping 6 and 6 will come maybe later, so let's
just stay with the numbering that we were just
recently given at the break. We're going to go to
5 and then we're going to go to the vote. Okay?

So number 5, discuss whether a risk evaluation and mitigation strategy, is necessary and would be able to ensure that the benefits of volanesorsen outweigh the potential risk of serious bleeding due to severe thrombocytopenia.

If volanesorsen were to be approved want to a REMS, discuss whether you would recommend any changes to the REMS presented by FDA.

Can I ask a question, FDA? Don't we have a slide on that? We certainly had it in an advance packet for the REMS by the FDA. Is there a slide? Perhaps we can open the discussion and they can find that.

I'm not sure it's that critical, but you refer to it in the discussion point.

DR. LaCIVITA: Go to Dr. Chapman's presentation and it was slide 13. Is that helpful or do you need more details?

DR. WILSON: If that's what you want us to leave up, let's leave that up. Okay? All right. So we're to discuss. This is what the FDA is
recommending, and whether a risk evaluation and mitigation strategy is necessary and would help to assure the benefits of volanesorsen outweigh the potential risks. That's the question.

Dr. Everett, clarifying?

DR. EVERETT: Just a quick clarifying question; a REMS registry -- I think what we're in part maybe interested in is the ascertainment of adverse events in an unblinded fashion in this population as they would move forward.

Is that the REMS registry or is that what the sponsor presented as a registry for all patients who would be on this drug?

DR. LaCIVITA: I can only speak for these two.

DR. EVERETT: Yes. The question is specifically about REMS registry.

DR. SHARRETTS: So the REMS registry would be each patient would be enrolled in the registry for the REMS. And that would collect patient information regarding information to help us better mitigate this risk. It wouldn't be, like, every
platelet count. It would be information basically
from the status form.

DR. EVERETT: So if there was an adverse
event, presumably that would show up on the status
form and then would be collected as part of the
REMS registry?

DR. LaCIVITA: Correct. That would be the
assumption. Thank you.

DR. WILSON: Dr. Neaton?

DR. NEATON: So all these forms come in.
Who's responsible for summarizing them on a regular
basis? I'm looking at the data.

DR. LaCIVITA: The sponsor.

DR. NEATON: That will be something that
would be required as part of the program?

DR. WILSON: Ms. McCollister?

MS. McCOLLISTER-SLIPP: I'm guessing that
there will be off-label use of this medication. I
mean, I know, if I had a kid that was 14 and they
were having lots of pancreatitis, I'd probably be
inclined to try to get them on the medication if
there weren't any other options.
But I mean, how does the REMS strategy as currently outlined deal with those issues? Is the off-label use going to be collected as part of the registry?

DR. LaCIVITA: The patient enrollment will probably collect information with regard to the patient's age, but the REMS strategy is really to mitigate the risk. It's not specific for off-label use.

MS. McCOLLISTER-SLIPP: It won't preclude off-label use?

DR. SMITH: Yes. I think that's fair. I think the way that we've discussed it, envisioned it, and based on some past experience, I would not count on the REMS to be a tool to prevent off-label use. We wouldn't be looking for that use.

MS. McCOLLISTER-SLIPP: But the registry would collect data from off-label use, so we would be getting data.

DR. LaCIVITA: So the registry would collect information on each patient that is receiving the drug.
DR. WILSON: Dr. Sinclair as well?

DR. SINCLAIR: I would say that, yes, a REMS is necessary. And I noticed from the sponsor's slide that the first prescription is tied to a platelet count, but then it gets a little unclear whether it's a monthly prescription or a 90-day prescription. I think they said monthly.

So anyway, I think it's important to keep an eye on the platelet count and hold the prescription if it's not where it needs to be in some way.

Also, about the registry, I would encourage consideration that you enroll a non-treated comparison group to shine some light on the type 2 thrombocytopenia. It's hard to interpret the results if you don't have a comparison group in a perfect situation.

People may go off, you could enroll them, and you can also try to understand the natural history of the disease better that way. People could become pregnant and that should be captured in a separate module. Personally, I would like to see it be restricted to the REMS. I liked the
adult patient part of the REMS. I don't feel comfortable with children being given the medication until they're evaluated.

That's all. Thank you.

DR. WILSON: Others? Dr. Raufman?

DR. RAUFMAN: Yes. I'm confused, but it's not the first time. I'm confused between what's up on that slide and what the sponsor is proposing because, if we go along with what the sponsor is proposing, it seems to limit off-label use because they're saying they're not going to ship drug unless a number of stipulations are met, including that it's an adult patient, confirmed diagnosis of FCS.

So that seems to me to limit off-label use. I would also add that I understand that the first episode of pancreatitis could be highly morbid, could even be lethal. But if there's a high risk to the drug, I'd rather it go to a high-risk population. And it seems to me that people who have had a previous episode of pancreatitis would represent a higher-risk population.
So I would include that in not only FCS, an adult with FCS, but an adult with FCS who's had an episode of acute pancreatitis. But I like their decision tree a whole lot better. It's just more detailed than what's up there.

DR. WILSON: So as I understand what Professor Raufman just said, he would consider especially including a history of pancreatitis as part of the study population, would be included in REMS.

You're getting close to our voting questions. Let's try to confine ourselves to the actual REMS principles, which is what the FDA wants.

DR. YANOVSKI: Yes. I want a clarification, too, because it sounds like what the sponsor had proposed was much more structured than the REMS that the FDA is putting out there, because that included again limitations as to which types of patients they would ship it to, routine platelet monitoring, whereas the REMS that I see here could be open to off-label use, which would mean you'd
get a broader population of points, maybe on other kinds of medications.

You wouldn't necessarily be getting as routine monitoring as the sponsor originally proposed. Am I correct about that?

DR. WILSON: Yes. Please identify yourself and speak.

DR. PIPPINS: My name is Dr. Pippins. I'm the deputy director for safety for the Division of Metabolism and Endocrinology Products. Could we please bring up Dr. Chapman's slide 15? So I want to remind the committee that we presented the REMS as currently envisioned by the FDA. The applicant has proposed additional activities in the form of a patient support program.

As has been noted, those additional activities are outside of the REMS and are not something that is accessible nor enforceable to FDA and that really pertains to our authorities under the law.

I want to highlight this slide, which talks about the REMS capabilities and the REMS
limitations. There's been some discussion, for example, about the issue of off-label use. And certainly, the committee in their voting discussion can talk about what they envisioned as being potentially an appropriate patient population, appropriate indication for this product.

But what I want to highlight here is, under the capabilities, we're talking predominantly about education of prescribers. We're talking about making patients aware. We are talking about collecting some additional data that might inform the safety risk moving forward into the future.

What we are not citing as something that the REMS will accomplish, what the REMS will not accomplish -- it cannot enforce monitoring as currently described in the prescribing information. That is not something that the REMS, as envisioned, can accomplish.

While the REMS can communicate what would be an appropriate patient population for prescribers, the REMS itself does not necessarily enforce on- or off-label use.
DR. WILSON: Is that helpful, Dr. Yanovski?

DR. SMITH: I'll just piggyback on one -- this is Jim Smith -- of the considerations regarding the off-label question. As you've heard this morning, there are probably a variety of opinions of how one would even make the diagnosis of FCS.

So one could envision an attestation that this patient has FCS. That could be interpreted many different ways by many different clinicians and I would leave it to you to consider how helpful in the end that would be.

DR. WILSON: Yes, Dr. Morrato?

DR. MORRATO: Yes, quick question then. So I know there are programs that are no blood, no drug, and those fall within REMS. I think I just understood that those aren't provisions. Is it because things are changing as to FDA's authority in this case or is it more or less your assessment of what seems the right appropriate burden, et cetera; given the situation, this is what you're recommending.
DR. LaCIVITA: We were trying to balance the safety with the burden here and it wasn't clear to us whether the additional requirements which ensure a greater degree of safety based on the complexity of trying to treat these patients.

DR. MORRATO: So that seems appropriate. Just since I asked the question, I'll just close the loop. I think, again, in the area of informing and knowing that patients are going to be on this potentially lifelong mechanism of updating that information or attestation and it's not like, once I started, that's the last time I get that information would be, I think, useful to build into.

DR. WILSON: Any further comments? Can I try to summarize? So this was a question of discussing the appropriateness of REMS. I did not hear any negative opinions. The first speaker, Dr. Sinclair, felt very strongly the REMS was necessary and most of the content was very supportive of needing REMS, but we have two versions put before us in our reading materials and in our presentations.
So there are principles, but there's also a little bit of uncertainty exactly what REMS might be because that's not fixed at this point and would be determined going forward.

There was felt very strongly a need in a REMS program to monitor, but we were reminded, especially by FDA, that the FDA is not in a position to, quote, "follow through" for, quote, "enforcement of that." There was especially a leaning towards use of these medications in adults and we've see no information in adolescent and pediatric groups.

It's not clear whether they would be included going forward and/or what might happen for outside of usual use, but for compassionate use and off-label use.

Let's see. There has been some interest especially in targeting perhaps individuals with a history of pancreatitis for future investigation and use because one of the secondary aims in the current study was the prevention of pancreatitis and it's been underpowered up until now to address
I think that's most of the issues. One was, we were reminded by the FDA that a REMS is largely an informational program. It does not enforce a program and it's a monitoring program. I still don't have resolved in my mind -- Dr. Morrato brought up the concept of no blood, no drug, meaning if you didn't get tested, that's something that would be decided by the providers and the care system.

It sounds like REMS would not be monitoring that, that FDA would be collecting data on that, but would be not quote, "enforcing" the no blood, no drug policy. Cynthia LaCivita, any further clarification?

DR. LaCIVITA: Just a point of clarification.

DR. WILSON: Yes.

DR. LaCIVITA: The FDA does have the authority to require monitoring prior to dispensing. The proposal that we have set forth is in the form of a status form, so that would be a
requirement they would need to submit that form every 90 days to provide that information.

What is not part of the REMS is the patient support program that the sponsor has suggested. It's a voluntary program where they're going to do home visits and other things to help facilitate obtaining platelet counts.

So that is a voluntary program that's being proposed by the sponsor outside of the REMS, so just a point of clarification.

DR. WILSON: Thank you very much. That's very helpful. I think we're ready to move forward. Now, we have 10 minutes left before the hour. We're going to vote as our next step, question 7. I'm going to read the question.

What's going to happen is, each person is going to vote and we vote simultaneously. So I'm going to give you the introduction to the voting system and then we're going to go.

So we will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and they will
continue to flash even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. And Commander Bonner will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state his or her name and also how they voted and that will go into the permanent record.

You can also state the reason why you voted as you did if you want. We will continue in the same manner until all questions have been answered and it's really limited here, so we're not going to have lots of questions, but we have two parts of this.

We actually have only one voting question, though. Does that make that clear? So I'm going
to read, as you can see here at the top, the whole thing. Based on the information included in the briefing materials and what was presented today, has the applicant provided sufficient efficacy and safety data to support approval of volanesorsen?

If yes, provide your rationale and any recommendations regarding the indicated patient population, dosing, clinical monitoring, risk management strategies, and/or post-marketing studies. If no, provide your rationale and comment on what additional data would be required to support approval.

Anything further before? Any questions? So your buttons are flashing. You all have a chance to vote. And remember the comments as we go around the room are going to be more important than you might guess because it really helps frame what goes forward from this meeting onward.

(Voting.)

DR. BONNER: For the record, for yes, 12, for no, 8, 0 abstained.

DR. WILSON: It's hard to read, but what
we're going to do next is, for those who voted,
we're going to go around the room. We're going to
start over to my right, which I can't read all the
names there. I'm sorry.

Meghan, you're going to start off, and then
Dr. Kane, and then Dr. Raufman, and we'll go in
that direction all around. So you're going to
start your name, how you voted, and if you would
like to supply a rationale for how you voted, that
would be helpful.

DR. ROWCLIFFE: Sure.

DR. WILSON: State your name first to start
out.

DR. ROWCLIFFE: Sure. So I'm Meghan
Rowcliffe. I voted yes. I think that there was
robust data to indicate that this drug is
effective. And I think that, if appropriately
monitored with the REMS that we've discussed, it
could be very beneficial to patients with this rare
form of disease. Thank you.

DR. WILSON: Yes?

DR. SMITH: Dr. Wilson? Jim Smith. If I
could remind folks, especially since we skipped
question 4, if you have any recommendations about
the indicated population that are different than
just familial chylomicronemia syndrome, this would
be the time to include that in your statement, just
since we skipped that discussion point. Thanks.

DR. WILSON: Yes. So next, let's proceed.

Dr. Kane?

DR. KANE: I voted no and, thinking about
it, if the population studied was comprised of the
patients who presented to us at 1:00, I think this
might have been a much easier discussion to have.

I had difficulty in extrapolating from the
reduction in triglyceride to a clinical benefit.
No question of reduction in triglyceride, but
that's the part that I'm certain about. The unmet,
I'm not so certain.

I almost don't understand the difference in
the experience as we heard at 1:00 versus what was
documented in the trial. The second problem I have
is that the population that we know about at this
point is still susceptible to a substantial risk of
severe thrombocytopenia.

While the REMS may help us, I do not know yet from the basis of any information that I can rely on the REMS that will create the safety that we need to. Thank you. And unfortunately, that's my ride to the airport.

DR. WILSON: Yes. We may excuse you, Dr. Kane. Thank you very much for your participation. Go ahead next, Dr. Raufman.

DR. RAUFMAN: Jean-Pierre Raufman. I voted yes, primarily for two reasons. I think, one, the sponsor provided compelling evidence that the drug lowers triglyceride levels substantially and I was swayed by the comments at the open session. I think that there is clearly a group of patients with this disease that would benefit highly from this agent. And based on that, I would recommend that the indicated patient population be more clearly defined as people with this disorder and the criteria for this disorder, there could be some definition of this disorder that doesn't require genetic testing necessarily.
There could be a threshold for triglyceride levels. There are experts in this field. We heard from several who I'm sure you could come up with a paragraph of a definition. And again, based on the fact that risk is relative, I think it's reasonable to limit use to people who meet the criteria for the condition and have had at least one episode of acute pancreatitis.

I'm not so sure about kids. I mean, there are kids who can have a very aggressive form of this disease and I wouldn't limit their access necessarily to this agent. I would put in a bunch of caveats, and safety features, and so on, but I wouldn't deny them treatment if they've got awful disease.

DR. YANOFSKI: Hi, Sue Yanovski. I voted no. And I did this feeling rather conflicted because I'm very cognizant that this is a rare, serious, and debilitating disease without other effective treatments.

I really want to see an effective treatment available and there's no question that volanesorsen
is effective in dramatically reducing triglycerides. However, I had a lot of concerns about whether the data presented by the sponsor actually established a favorable risk-benefit ratio.

I was concerned about the large number of dropouts, that people had a dropout because of SAEs or lack of tolerability and lack of data on the dosage regimen that they've actually proposed. I also wish we could have seen some sort of improvements in patient-reported outcomes like pain or quality of life.

Finally, I'm concerned with the REMS. I'm concerned that, once this is on the market, we're going to see a lot more off-label use and in patients in whom it wasn't tested. And I don't really know how to prevent that once it's on the market.

I'd really like to see further data using the proposed dosing. I'd like to see more safety data and I'd like to see more data on clinical and patient-reported outcomes.
DR. ORTEL: Tom Ortel. I voted yes. I voted what I considered to be probably a qualified yes. I do think it is important that we establish the diagnostic criteria for who should be getting the drug. In hematology, we're using next-gen sequencing more and more to characterize rare diseases.

I think that actually looking into having that as a requirement is not an unreasonable step. I think that there needs to be some better clarification in the REMS between what the sponsor is putting together, what the FDA is putting together to clarify some things and some of the other concerns I had about treatment recommendations, I think, need to be addressed.

But as far as lowering the triglycerides and the impassioned statements at 1:00, I think that that's why I voted a qualified yes. And I have to get to the airport, too.

DR. SHAMBUREK: I'm Robert Shamburek and I voted yes. I must first commend the applicants, both of them, for pursuing a rare lipid orphan
disorder which is frequently neglected. Enrolling 66 patients in an orphan disorder is very impressive. Volanesorsen impressively lowered triglyceride in familial chylomicronemia syndrome in a very desperate unmet need for these patients. The levels of triglyceride below 750 to 1,000 should offer significant improvement in clinical events in the orphan disorder.

I believe there will be benefit for pancreatitis and other clinical symptoms, but I don't think the CS6 pivotal was powered in order and also had lower-risk patients that wouldn't show up in 1 year.

With that said, there are safety issues of platelets and bleeding that are a major concern. We've heard there's predictable and underpredictable ways of following this.

If the risk is deemed significant by either the FDA or the physician, there may be a need for more stringent criteria such as the need for recurrent pancreatitis, noting that one episode can be fatal, but we have to do the risk-benefit.
I think the dosing recommendations for what we know now, which has been stated as very limited, is what we'd have to propose. The REMS follow-up is very important. Risk management strategies should certainly include the platelet, immunologic, and bleeding issues. The post-marketing should focus on the platelet, bleeding, and pancreatitis events.

I think there is a need to get this into kids somehow, but there still remains a major issue of, I think, for safety with weight and dosing that are lacking and I don't think can be extrapolated.

So I voted yes, that patients should be informed of the current unpredictability of platelets and bleeding risk, and know there is the REMS to help us out and weigh that against the unpredictable pancreatitis risk.

MS. CUARESMA: Nichole Cuaresma. I voted yes. I wish I could just say what he said and you can put that on record because it's going to sound better than what I'm going to say, but it's very similar in that this orphan drug is obviously
limited to a very rare population, two of which live in my home.

So the primary endpoint was to reduce the triglyceride level, which it did, and I think the risk versus benefit is going to be different for each patient. And again, I'm not a medical professional, but the mutations in one of my family members is different, a little different than the other.

One is very extreme and needs this ASAP and the other maybe won't. So I think each case is going to be different and even more rare than the other in some cases. And I think it's up for the patient and the adults decide on whether or not they want to take this medication in the end.

So the close monitoring, I definitely agree with, and the REMS. In fact, I liked the more detailed monitoring that the sponsor had put up. And the two-week blood draws, I think, is important, although I will say that, for pediatric use -- and I do have a two-year-old and I know there's not very many infant patients that are
recognized in the United States at this point, but I don't quite feel comfortable with where this is at right now for pediatric use.

But again, in an adult, I would say that I would agree continuing or the orphan drug as it stands. Thank you.

MS. McCOLLISTER-SLIPP: This is Anna McCollister-Slipp. I voted yes. And there are lots of things with the data that was presented that I didn't think were where I would like to see it. It's an incredibly small population.

I know designing studies for rare disease can be very difficult in terms of both powering, recruitment, retention, et cetera. And I think there's a lot of data that's missing. I'm intrigued by the fact that we got a decrease in the biomarker, which is important and apparently clinically significant, but we didn't see any changes in pain and the numbers of pancreatitis as me as a patient, if I were faced with it, would be sufficiently convincing, but they weren't brilliant.
So having said that, as a patient who takes 16 different medications, 3 of which had a really hard time getting approved and making it through advisory committees, I'm a big believer in the perfect, particularly perfect dataset not being the enemy of the good and the clinically helpful.

I think that patients who live with a debilitating long-term disease could get really smart on that and, if they're working with their physicians -- and I think most people who live with that kind of a condition would be - they get pretty good at evaluating the risk-benefits.

If the drug doesn't work, if the benefits don't outweigh the risks and the burden, they won't take it. So I think we should be collecting lots of data and figuring out which populations are best, so that we can have better guidance for physicians and clinicians and patients moving forward.

In terms of the REMS strategy, I think it's absolutely critical. You have to have education. I mean, monitoring seems to be really important.
And I would just caution that the least burdensome, the least restrictive you can be, the better just because those kinds of things have a way of getting calcified through the insurance system, which can create significant burdens on patient and can create significant barriers to access.

What that would mean in this particular case, I don't know, but I have to live with that with at least one of the medications I take. And in terms of ways to do that, there are some really clever uses in digital health, consent forms where you have quiz-based consent.

I really like the idea of reconsenting just to make sure that people continually stay aware of the risks and make sure that the risks are top of mind, not in a way that's burdensome or obnoxious, but there's some good models out there that you could look at.

DR. BURMAN: Ken Burman. I voted yes. It is always difficult to balance the risk of disease versus the risk of the particular medication. This balance is especially difficult in orphan diseases,
where we have to compromise our desire for an
optimal study with real-life issues, such as for
example the number of patients that can be
recruited in a study and how long they can be
studied and analyzed long term.

The central point to me is this disease is
caused by an elevated triglyceride and the sponsor
definitely showed that the agent was successful in
lowering triglyceride s that I would expect all the
other sequelae that may be related to elevated
triglyceride to be abrogated with the medication.

I'd also like to commend the sponsor and the
FDA for their presentations, which were excellent.
I strongly believe in the REMS study that was
mentioned, the more detailed one.

I have strong views that I think that the
FCS definition is a little vague, although genetics
doesn't prove that everyone has it. I think
genetics analysis should be initiated in every
patient and, if it turns out to be negative, then
strong clinical judgment in addition.

I raised the issue of a post-marketing study
that would look at many of the issues we've
discussed today with regard to different dosing and
quality of life issues. And I also commend the
open session speakers for their impassioned
comments.

DR. MORRATO: Elaine Morrato. And I also
voted yes in favor. Clearly, there's a strong
unmet need for a rare genetic condition with great
suffering as we heard, significant physical,
emotional, and financial burden of the disease.

It came down to me -- I think we were being
asked to trade off two potentially life-threatening
conditions, the pancreatitis as well as the drug-
attributable thrombocytopenia. Unfortunately, we
had limited information on both of them.

But I think, at the end of the day, I felt
that, for some patients, the trade-off to avoid the
pancreatitis risk made sense given their personal
history. But recognizing that, for others, that
may not make appropriate benefit-risk for them.

So I ended up erring on the philosophy in
this particular situation, following more of a
compassionate use kind of program and the desire to support patients to make informed decisions.

Having said that, though, I think patients should be aware there's a 1 in 10 risk, 9, 10 percent of the patients fell below 50,000, a 1 in 20 risk of below 25. And so sometimes, in our enthusiasm of hearing the promise of the efficacy, we don't always hear the downside risks as well.

So I really want to make sure that the REMS program is rigorous and strict in that regard, that there's appropriate informed consent. I think it still wasn't so clear to me the regulatory teeth on the 90-day status form. I think there needs to be some consequences tied with dispensing to make sure that system doesn't get out of control.

In terms of the frequency of reporting, I know REMS can set the standard of reporting timeliness. I would expect it to initially be quarterly as opposed to on a longer time frame. And I think patients as well as providers need to know going in that the monitoring itself is not necessarily going to mitigate the risk.
I see greater value in its pharmacovigilance and understanding of the risk profile value as opposed to it is a strong risk mitigation in itself. But at the end of the day, I believe that, in real-world prescribing with a strict REMS like this, as we've seen in other programs, it will be self-limiting to which centers or clinicians and patients, particularly the centers and clinicians that will actually sign up for this, we already know.

With a few hundred Americans having this condition, it's already being concentrated among a few providers that treat. So I think, at the end of the day, largely the centers that were doing the trials will probably be the centers providing care. But a last comment I wanted to include is that I am concerned of the cost of this. We don't talk about cost here.

But to patients, we heard from some in the open forum how the disease has bankrupted their families, but we're also hearing more and more in the news about narrowly targeted drugs that charge
hundreds of thousands, if not millions of dollars a year.

I'd hate to see a trade-off of where it's saving costs in one area only to be adding costs in another area.

DR. BUDNITZ: Dan Budnitz. I voted yes for approval, but if there were another treatment option for FCS, I probably would not have voted yes based on the trial data that were presented.

I think I want to make three points. One is, as folks have mentioned, the efficacy and safety data are extremely limited, a few patients in relatively short follow-up for a lifelong period. I'm also concerned about the unknown mechanism or mechanisms of thrombocytopenia and I do worry that, over the course of lifelong therapy, more patients are likely to experience thrombocytopenia than events of pancreatitis avoided.

But it's hard to gauge the relative value from each of those conditions. I did note some concern over the potential signal, anaphylaxis, and
serum sickness. That was brought up. But I think the only way to understand that better is with more data.

One other point about the safety data that was submitted, I think, really was -- the analysis was compromised by the high dropout rate. I mentioned that before, but I agree with the FDA reviewer that, the measure of efficacy is probably biased due to the high rate of treatment discontinuation, but I think that also applies to the adverse event rates as well and, in particular, when essentially there's no dropouts of the placebo group but very high rates for the treatment group, it's kind of like an incidence density for adverse drug events, would be a useful measure to include in the future.

Then finally, I do appreciate the sponsor's stated commitment to have their risk mitigation program. I think that is critical to have that centralized coordination, and laboratory testing, and reporting to clinicians before dispensing, because I do think that this is really the only way
we'll get more information about the efficacy, effectiveness, and adverse events.

One thing that could be done is enrollment. While there may be some debate of definition of FCS when enrolled, documentation of clinical symptoms, triglyceride level despite adherence to low-fat diet, failure of other therapies, and history of pancreatitis, abdominal pain documented, that would be helpful.

Finally, the logic behind biweekly platelet testing may be lacking, but it seems like the reasonable approach again to limit the time that patients might be idiosyncratically thrombocytopenic while taking other medications.

DR. WILSON: Peter Wilson. I'm supposed to vote next, but Dr. Epstein has to go, so he's going to tell us how he voted and then come back to me.

DR. EPSTEIN: My apologies. I have an emergency. Someone swallowed a box of razor blades. So I voted no even hearing the passion of the people with FCS, because there's always a risk-benefit ratio and, really, here I believe we're
trading one disease for another in a population
that wasn't studied for the condition for which we
say that we're going to help.

We didn't show clinical benefit, but we
showed a serious adverse event, which is yet
another new clinical disease. And in my
experience, we've had drugs before that have
created new clinical problems that, in my
experience with previous committees, have been
withdrawn for much, much less numbers of adverse
events into the 1 in 1,000.

But here, we have something that's causing a
new disease, thrombocytopenia. There's also the
serum sickness, the anaphylactic shock, these very
high rate of injection site reactions which need to
be addressed, maybe with the formulation.

There's still questions about the dosing,
the dosing intervals, the monitoring. And then
there was the main thing I think which was the high
dropout, which I think makes it very difficult to
actually correctly analyze this data.

So all in all, I thought that it was a
yeoman's effort to get to this point, but it missed
the mark. And I apologize for leaving.

DR. WILSON: Thank you very much. You're
gone. Dr. Epstein had to leave. So Peter Wilson;
I voted yes. I'm not going to repeat the other
reasons that have been voiced before. I want to
make some suggestions to how we might move forward.
Number one is to collect more metabolic data for
people as people are being recruited into either
studies or registries, which means comprehensive
laboratory data and a laboratory database that will
be able to be explored multiple times as we go
forward for both proteomics and genomics because
we're going to potentially redefine this disease
each year or ever few years as we find more genetic
and other variants related to hypertriglyceridemia
and not only at the outset, but also for anybody
who experiences a serious adverse response,
especially for thrombocytopenia, also to collect
another specimen there and to have a special
registry database where molecular scientists can
investigate this.
So that's number one. Number two is, I favor two post-marketing studies and one would be, as has been mentioned before, is patients who have already had pancreatitis and to see whether this molecule prevents pancreatitis.

I believe we may have an estimate in the range of 400, perhaps more than that, person-years of exposure may help to address this question and, with larger experience, we may be able to get an answer, especially starting with people who have already experienced pancreatitis once.

Then secondly, I think an area of special concern is pediatrics, but especially when we get into the adolescence, where they could consent themselves and they may have already multiple episodes of pancreatitis. It's to do a safety study in, let's say, post-14-year-olds, because some of these have had multiple episodes of pancreatitis and have had molecular diagnosis at that time.

That would move it forward and not just with a registry, but with a post-marketing at least
safety study and perhaps outcomes study. So I'm done.

DR. EVERETT: This is Brendan Everett. I voted no. It's a qualified no. I think, to use Dr. Yanovski's comment, it was a difficult no. And I think a lot of us have applauded the sponsor for their efforts in bringing the drug forward.

I want to add perhaps some less laudatory comments in the sense that I think they also made some critical missteps early in the development program, for example in not choosing to move forward with two doses instead of one or with different dosing frequencies that would have informed the decision that we made today and made it much easier, A, to understand the risks, B, to understand the benefits on the alternative dosing regimen that they have proposed and C therefore allowed me at least to potentially vote yes.

I think I'm satisfied that, with the dose, A, there's a clear unmet medical need and we heard that. And importantly, there's evidence that the dose that was used in the study, albeit with
significant dropout, caused substantial reductions in triglycerides.

I don't know what the proposed dosing regimen will do either in terms of benefits or risks and that's one of the key reasons for my vote no.

I think, as I mentioned, there's an important role for this medication in the right population and that's really the source of my hesitation in voting no, the people that we heard from earlier, because even if there are people with this condition who take the medication and find that they can't tolerate it, there are other people who find that they can.

For those patients, it offers significant benefits clearly. I want to note that choosing who those patients are is very difficult and this gets to question 4. In particular, the study of 66 patients had 9 patients who were subsequently identified to not have FCS by the study-specific criteria that were used, so that's 14 percent of patients enrolled in the clinical trial program.
That being said, we've been in this room or a similar room and discussed heterozygous FH and diagnostic genetic tests for that condition. And we have a similar problem with multiple mutations, undiscovered mutations, and it is extremely cumbersome for clinicians to use that kind of genetic data to actually make a decision and then frankly to get it through the various payment mechanisms to get the drug for the patients who they strongly feel needed.

So I would be reluctant to require a genetic test as part of the labeling because, even if it's a suggestion, it ends up being picked up by the payors and ends up becoming sort of the de facto rule because the drug, I anticipate, will be expensive.

So lastly, I think the REMS is a key part of the safety monitoring because I think the data that we have from the open-label extension is essentially biased because the enrollment into that study is amongst people who did well when getting the drug in the first trial.
So we're not getting an adequate sense of what the true risks and benefits are in that particular population. That's a population who tolerates the drug and is interested in getting it going forward. So with that, I'll stop.

DR. WILSON: So if I could jump in, Dr. Newman, you have to go, so can we have you vote next?

DR. NEWMAN: Thank you. This was a very difficult decision for me because I know how difficult life is for patients with familial chylomicronemia syndrome. But I looked at the question literally, which is, has the applicant provided sufficient efficacy and safety data to support approval of volanesorsen.

I felt that, although there was a significant reduction in triglycerides with the dose used, which may not be the dose used in clinical practice, that there was no clinical benefit on either pancreatitis, abdominal pain, or on any other symptoms and signs that these patients might have. But my real concern was the benefit-
risk ratio.

I thought that the risk was too severe, the risk of bleeding, obviously. And this may not be predictable in certain instances and it could cause a life-threatening bleed.

So I also thought that the dosing regimen that is going to be used has not been adequately studied, so therefore, we can't really evaluate the benefit-risk and know how effective it is in reducing triglycerides and whether it would mitigate the risk of thrombocytopenia and bleeding.

But I think that, had the question been different, I might have voted a different way because there is a need for this drug, but I didn't take that into consideration in my answer. And I think that more efficacy and safety data would be extremely helpful and I think we need more placebo-controlled trials using the new dosing and platelet monitoring regimen and a particular emphasis on safety for longer periods.

So that explains my vote.
your name and how you voted for the record. Thank you.

DR. NEWMAN: My name is Connie Newman and I voted no.

DR. STRONCEK: I'm Dave Stroncek and I voted yes. The data shows that the drug is effective for lowering triglycerides. The safety profile of the drug, though, is very problematic, not only the thrombocytopenia, risk of bleeding, but the risk of serum sickness, hypersensitivity, and skin reactions.

Despite this, I voted yes because there's no other treatment available for this patient population. I think, though, because of all the safety concerns, it is critical to move forward with a robust risk mitigation strategy, which would include biweekly platelet counts or platelet tests. I think it's also important to encourage data collection and data analysis in further studies so the whole list of questions that we're all asking can maybe be addressed in the future.

DR. WEBER: This is Tom Weber. I voted no.
Again, I'll try to be brief. I think it's been stated this is a significant and serious condition with potentially life-threatening complications as pancreatitis.

It was a difficult decision for me, but again, I try to balance risk and benefit in the nature of the question that was asked. And I had some concerns. I think specifically I had concerns about the study population that was included in the trial and may not have represented the real-world experience of this and, even though it met the primary endpoint, didn't show at least in the concern in terms of improvements and concerns over pancreatitis or some of the GI symptoms.

I also have concerns about the frequency of thrombocytopenia in the study and don't believe at this point that a REMS program can anticipate or identify the more idiosyncratic events that can occur, so there's a particular concern there.

More minor but still concerning is the rate of cutaneous events, and hypersensitivity, and also GI, liver-related events. And that may be
reflective of the underlying PK of the drug, which we know accumulates to a greater degree within the liver.

Then probably most importantly, the efficacy as proposed for the treatment strategy based on weight and based on every-other-week dosing really hasn't been proven and I don't think warrants approval of the drug.

The data was encouraging in terms of the dose adjustments, but that wasn't the way that the study was set up, so I'm concerned about that. As far as where to go from here, I think that studying it in a more defined fashion in terms of every-other-week dosing or perhaps reduced dosing of 200 milligrams weekly, which in the phase 2 trials did show very good efficacy with regard to triglyceride lowering, would be a good step.

The other thing that I came away from the data is that it looked like the thrombocytopenia events occurred primarily after 90 days, not necessarily some of the idiosyncratic events, but perhaps intermittent dosing of 3 months on,
3 months off because the long half-life of the drug could be an approach that may be safer for a lifelong therapy where there are still serious concerns.

As far as identifying subjects or patients for this that are stratifying, there's a recent review of this condition, of FCS, and perhaps trying to define it separately from familial combined hyperlipidemia with apoB testing, which is commercially available.

So some other things can be done to try to better define a population, I think, and who is going to benefit from this therapy.

DR. LOW WANG: My name is Cecelia Low Wang and I voted yes. This was really because I think the sponsor has demonstrated marked triglyceride lowering and I was encouraged by the fact that there was no major bleeding, although there was 1 patient with platelet count of less than 10,000.

There are no other effective therapies and I really wanted to make sure that there was access to therapy for this rare and debilitating disorder.
Just a few points; just in terms of balancing benefits and risks, I do think that the indication for the drug should be patients with FCS with quality of life significantly affected by the hypertriglyceridemia. That could include pancreatitis within the past year.

Also, I think the current dosing proposal and monitoring is reasonable, but will not prevent type 2 thrombocytopenia, as mentioned before. I was very impressed by the REMS proposal that was proposed by the sponsor. And I hope that can be done.

I think that the label needs to include some type of warning about concomitant antiplatelet or anticoagulant therapies and the need for renal function monitoring and proteinuria monitoring.

As has been mentioned, I think that there are a number of studies that need to be done. And so there’s a lot of information that we’re still missing, requiring a post-marketing study with a hard deadline in a selected population of patients to better assess the safety profile, including the
hypersensitivity reactions using bleeding as a safety endpoint.

Looking at platelet function, quality of life measures, trying to decrease the injection site reactions, trying to figure out the mechanisms for the thrombocytopenia and trying to figure out what's happening with the platelet function.

But I do think that this is life changing in select patients, as I mentioned before, and this is why I voted yes, but we need a lot more information.

DR. NEATON: Jim Neaton. I voted no. So I think potential benefit of this drug could be large, but the realized benefit is uncertain. There are some major safety concerns and our ability to mitigate those safety issues is also an uncertainty.

When I look at overall risk-benefit, it doesn't seem to stand up and, when I look at the patient dropout in the study and the number or percent that went onto open label, then dropped out in open label, I think the study participants are
telling us that.

Now, I thought about voting yes and recommending a different high-risk population. I guess that was an option as well. But then we don't have the data on risk-benefit for that population.

So I'm left with kind of a recommendation that this potentially is a very good drug, but it should be studied in a much higher-risk population given the known risk.

DR. SINCLAIR: Hi I'm Susan Sinclair and I voted no. I would have liked to have voted yes, but I took the question literally as well with sufficient efficacy and safety data presented. Efficacy was certainly impressive for the surrogate endpoint, but I did not see clinical benefit beyond surrogate endpoint.

Also, the REMS cannot adequately mitigate the risks of the unpredictable decreases in platelet count. And the high discontinuations again suggest some sort of perhaps unmeasured satisfaction.
The pre-market signals of course bothered me the most, but I do know that there's being data collected as we speak, so I'm hopeful that, that will shine some light on this potential signal and that something can be approved for this population, but based on the question, I voted no.

**Adjournment**

DR. WILSON: We're about done. We give the last word to the FDA. Any comments from our FDA leadership?

DR. SMITH: I think I have no additional comments. I'd like to thank you all for a very robust discussion today. It was incredibly helpful for us.

I think, even the questions that we skipped over, you were able to work in comments. So that's helpful. As you got a sense, this has been a very challenging application for us and we get that it was not easy for you, either. So we have something in common.

So thank you all very, very much for your time and we'll see you next time.
(Whereupon, at 5:34 p.m., the meeting was adjourned.)