FDA Briefing Document

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

May 10, 2018

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought NDA 210645, Waylivra (volanesorsen) injection for the treatment of familial chylomicronemia syndrome to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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MEMORANDUM

DATE: April 13, 2018

FROM: James P. Smith, MD, MS
Deputy Director, Division of Metabolism and Endocrinology Products (DMEP)
Office of Drug Evaluation II / Office of New Drugs
Center for Drug Evaluation & Research

TO: Members and Consultants, Endocrinologic & Metabolic Drugs Advisory Committee (EMDAC)

SUBJECT: EMDAC meeting for volanesorsen (Waylivra)

Thank you for agreeing to participate in the May 10, 2018, advisory committee meeting. This meeting is being held to discuss the safety and efficacy of volanesorsen as an adjunct to diet for the treatment of patients with familial chylomicronemia syndrome (FCS), which is the subject of a new drug application (NDA) submitted by Akcea Therapeutics, Inc.

Volanesorsen is a modified phosphorothioate antisense oligonucleotide (ASO) that targets apolipoprotein C-III mRNA, leading to its degradation and subsequent reduction in the synthesis of this protein. ApoC-III has a significant role in regulating plasma triglyceride (TG) levels by inhibiting both lipoprotein lipase (LPL)-mediated hydrolysis of TG-rich lipoproteins as well as hepatic lipase activity. Elevated apoC-III reduces the clearance of TG-rich lipoproteins from plasma, resulting in hypertriglyceridemia; therefore, reduction of apoC-III would be expected to lower plasma TG by facilitating clearance.

As you will read in this briefing document, the review team is in agreement that volanesorsen markedly lowers fasting TG in patients with FCS, a rare syndrome that currently lacks approved pharmacotherapy. Changes in fasting TG have been used to support approval of drugs intended to treat more common forms of severe hypertriglyceridemia (generally defined as TG ≥500 mg/dL) for several decades, on the assumption that lowering TG will reduce the risk of pancreatitis among patients with this degree of TG elevation.

When efficacy is established via an effect on a surrogate endpoint, however, true clinical benefit typically remains unknown; therefore, the benefit/risk assessment must balance an unmeasured clinical benefit against the known and potential risks of the drug. At the time of the volanesorsen end-of-phase 2 meeting, the Division recognized that limited data collected during early-phase trials did not provide adequate reassurance regarding the safety/tolerability of volanesorsen. Thus, the applicant was strongly encouraged to consider assessing outcomes that are meaningful to patients with FCS (e.g., abdominal symptoms), since demonstrating an effect of volanesorsen on how a patient with FCS feels or functions would strengthen the application by better informing clinical benefit. The applicant incorporated a patient-reported outcome instrument to assess abdominal pain on a 0-10 numeric rating scale, added health status questionnaires routinely used in clinical trials (SF-36 and EQ-5D), and adjudicated events of pancreatitis. Refer to the statistical and clinical reviews for further discussion of these endpoints and analyses, since we are interested in how these data impact your thinking with respect to the magnitude of the potential clinical benefit(s) of volanesorsen.

Despite the magnitude of the effect observed on TG, the volanesorsen review team remains uncertain whether the benefits of volanesorsen outweighs its risks, considering safety concerns with this product. Although the reviews

highlight several safety/tolerability issues, the primary focus for both the applicant and the reviewers has been the risk of thrombocytopenia and resulting potential for serious bleeding. As you will read in the FDA hematology consultant's memo, drug-induced thrombocytopenia is a well-known adverse event associated with exposure to ASOs in preclinical animal studies and clinical trials, although the underlying pathophysiology remains unexplained. Most patients exhibit a gradual decline in platelet count that is typically mild; e.g., in the pivotal FCS trial (CS6), a ~30% decline in platelet count, on average, was observed within the first 6 months among patients treated with volanesorsen. More concerning, however, is the observation that some patients can exhibit a rapid and unpredictable reduction in platelets to extremely low levels. In CS6, no patients assigned to placebo had a platelet count fall below 100,000/uL compared with 18 (55%) of 33 patients assigned to volanesorsen. Three (9%) of 33 patients had a platelet count <50,000/uL, including 2 patients with a nadir <25,000/uL. Across the development program, 9 volanesorsen-treated patients have had platelet counts <50,000/uL; four of these events, including 2 patients with platelet nadirs of 15,000/uL and 17,000/uL, occurred despite enhanced platelet monitoring, which was as frequent as every 1-2 weeks, and dosage adjustments. Switching to biweekly dosing and/or dose interruptions have not always led to a sufficiently timely recovery of platelet count; some patients have required treatment with prednisone, hospitalization, and/or administration of IVIG. To date, serious bleeding events have not been observed in this relatively limited safety database, but the reviewers highlight a higher risk of non-serious bleeding-related adverse events with volanesorsen (e.g., epistaxis, petechiae). Some of these events occurred at platelet levels where spontaneous bleeding would be unexpected, suggesting the possibility of an abnormality of platelet function as well as an effect on platelet count.

After the NDA review was well-underway, the applicant unexpectedly submitted an amendment that proposed a new dosing and platelet monitoring strategy for labeling that had not been implemented in any of the clinical trials. The applicant now proposes that dosing recommendations vary by body weight (above or below 70kg) and recommends platelet monitoring to occur at least every other week (more frequently if platelets fall below 100,000/uL). Reviewers from the Office of Clinical Pharmacology have taken the lead in reviewing the rationale and support for this newly proposed dosing strategy; please see their memo for details. Regarding platelet monitoring, the review team (including the hematology consultant) questions the feasibility and effectiveness of a monitoring scheme of this intensity for a lifelong therapy. At present, we have no evidence that the risk of severe thrombocytopenia diminishes with time; the onset of platelets falling to <50,000/uL has ranged from 51 to 300 days in this program. Furthermore, Dr. Roberts notes in her clinical review that the most recent case of a patient with a platelet nadir of 17,000/uL occurred despite weekly platelet assessments.

Although not the only safety issue (see Dr. Roberts's review), the potential risk of serious bleeding due to severe thrombocytopenia associated with volanesorsen has led the review team to propose that if volanesorsen were to be approved, a risk evaluation and mitigation strategy (REMS) would be required to ensure that the benefits of volanesorsen outweigh its risks. Please see the memo from the Division of Risk Management in this briefing document for a discussion regarding FDA's proposed goals and components for a REMS for volanesorsen. It is important to note, however, that FDA has not yet concluded that the benefits of volanesorsen for its proposed use would exceed its risks even with a REMS in place; therefore, your discussion and input regarding this application will be extremely valuable.

We sincerely thank you for your service and commitment to consider this application. We look forward to your discussion and advice regarding the potential approval of volanesorsen.

Draft Points for Discussion

1. A reduction in fasting triglycerides (TG) has been accepted by FDA as an endpoint that can establish efficacy for several classes of drugs intended to treat patients with severe hypertriglyceridemia (TG >500 mg/dL), since lowering TG in this setting is expected to reduce the risk for acute pancreatitis. When efficacy is established via an effect on a surrogate endpoint, uncertainty generally remains regarding the magnitude of the drug's effect on true clinical benefit (i.e., how patients feel, function, or survive). The expected type and magnitude of clinical benefit(s), however, are important to consider when making a benefit/risk assessment.

   Please discuss the efficacy of volanesorsen in patients with familial chylomicronemia syndrome (FCS). To what extent are you convinced that reducing TG levels with volanesorsen will have a favorable impact on FCS? How would you characterize the magnitude of clinical benefit that results from treatment with volanesorsen?

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 you have identified.

3. Discuss the risk for thrombocytopenia associated with volanesorsen.
   a. Discuss your level of concern for the risk of thrombocytopenia and related bleeding with chronic treatment with volanesorsen.
   b. The applicant has proposed labeling that recommends intensive platelet monitoring (i.e., a minimum of every 2 weeks for the duration of treatment with this potentially lifelong therapy). Discuss whether the proposed frequency of monitoring adequately addresses the risk of thrombocytopenia, as well as whether such monitoring would be feasible in clinical practice. If you disagree with the proposed monitoring scheme, discuss how you believe patients treated with volanesorsen should be monitored for thrombocytopenia/bleeding, if approved.
   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 that would ensure the safe use of volanesorsen.

4. Discuss whether "familial chylomicronemia syndrome," without further definition, is sufficiently specific to describe a patient population for whom volanesorsen treatment should be considered for approval.

5. Familial chylomicronemia syndrome can have the onset of symptoms in childhood, yet no pediatric patients have been studied in the volanesorsen development program. Discuss your level of concern with respect to the potential use of volanesorsen in this population if approved for adults and any recommendations you may have for future study in the pediatric population.

6. Discuss whether a risk evaluation and mitigation strategy (REMS) 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 with a REMS, discuss whether you would recommend any changes to the FDA-proposed REMS.

7. 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?
    a. If yes, provide your rationale and any recommendations regarding the indicated patient population, dosing recommendations, clinical monitoring, risk management strategies, and/or post-marketing studies.
    b. If no, provide your rationale and comment on what additional data would be required to potentially support approval.

Clinical Review
Endocrinologic and Metabolic Drugs Advisory Committee Meeting
May 10, 2018

New Drug Application 210645: Volanesorsen
Applicant: Akcea Therapeutics
Clinical Reviewer: Mary Dunne Roberts, MD

Executive Summary

Background

Familial Chylomicronemia Syndrome (FCS) is a rare, autosomal recessive condition affecting 1 to 2 individuals per million. FCS is due to biallelic pathogenic mutations in the enzyme lipoprotein lipase (LPL) or its cofactors, which results in absent or severely reduced LPL activity leading to inadequate processing and clearance of triglycerides, primarily from chylomicrons. Individuals with FCS have persistently elevated levels of triglycerides (TG), which increases their risk of pancreatitis. Pancreatitis is the most serious and potentially life-threatening consequence of this condition; however, not all patients with FCS experience pancreatitis.

FCS usually presents in childhood or adolescence, but the diagnosis may be delayed due to the rarity of the condition and varying severity of clinical presentation. Reported symptoms include episodic abdominal pain, fatigue, cognitive impairment, depression, and anxiety. In addition to pancreatitis, clinical signs include eruptive xanthomas, lipemia retinalis, and hepatosplenomegaly. A diagnosis of FCS is suspected based on clinical characteristics and lipemic blood in the fasted state. Broad consensus is lacking on specific diagnostic criteria. For example, proposed thresholds for TG to suspect the syndrome range from >750 mg/dL to >2000 mg/dL. The workup typically includes ruling out other common causes of TG levels in this range (such as diabetes mellitus and obesity). A history of acute pancreatitis (as adult or child), recurrent abdominal pain without definable cause, eruptive cutaneous xanthoma, and hepatosplenomegaly all support the diagnosis. Diagnosis is confirmed by molecular genetic testing and, in some specialized centers, by the detection of low or absent LPL enzyme activity.[1]

Currently, a restrictive low-fat diet (<20 g fat) is the mainstay of therapy and can be quite effective. A 29-patient case series published from the University of Cape Town notes, "All patients displayed a marked decrease in plasma triglycerides after dietary treatment. The mean worst triglyceride of 56±41 mmol/l [4960±3631 mg/dL] fell to 10.9±8.8 mmol/l [965±779 mg/dL]…Follow-up data are incomplete because patients with good dietary adherence generally obviate pancreatitis and remain well. Patients who adhered to diets restricting triglyceride to <10 g/d for short periods achieved fasting triglyceride concentrations of

[1] Burnett JR, Hooper AJ, and RA Hegele. "Familial Lipoprotein Lipase Deficiency." *GeneReviews*, last updated June 22, 2017. https://www.ncbi.nlm.nih.gov/books/NBK1308/

<6 mmol/l [<531 mg/dL]."[2] TG-lowering drugs, such as fibrates, are generally not effective in reducing TG in this population, and there are no FDA-approved products for the treatment of FCS.

Volanesorsen, herein referred to as VLN, is an anti-sense oligonucleotide inhibitor of apolipoprotein C-III (apoC-III), a key regulator of TG metabolism via LPL dependent and independent mechanisms. VLN acts by inhibiting apoC-III production, thereby decreasing the negative effect of apoC-III on TG clearance, lowering TG levels.

On 30 August 2017, the applicant, Akcea Therapeutics, submitted a New Drug Application seeking an indication for VLN as an adjunct to diet in patients with FCS. The proposed dosing regimen initiates VLN treatment at 300 mg/week delivered subcutaneously for 3 months, followed by adjustment of the dosing interval based on body weight and platelet count. While treated with VLN, patients are to have their platelet count monitored at least every two weeks, presumably for the duration of this potentially lifelong therapy.

The primary data source for evaluating the efficacy and safety of VLN 300 mg/week is CS6-pivotal, a placebo-controlled Phase 3 trial in adults with FCS. Two additional Phase 3 trials provide supplemental safety data for VLN: CS7-OLE, an ongoing open-label extension study in patients with FCS, and CS16-HTG, a 6-month placebo-controlled Phase 3 trial in patients with severe hypertriglyceridemia (TG ≥500 mg/dL).

The initial dosage for the phase 3 program, 300 mg/week, was based on non-clinical data and efficacy and safety analyses from a phase 1 single/multiple dose study in healthy volunteers and a 13-week phase 2 dose-finding study in 88 patients (64 VLN/24 placebo) with hypertriglyceridemia. At the End-of-Phase 2 meeting, the Division strongly cautioned the applicant about moving into Phase 3 with a single dose, given the limited safety/tolerability experience with 300 mg/week in early-phase studies.

The applicant submitted an unsolicited revised dosing regimen approximately 5 months into the 12-month review cycle (on January 24, 2018). The review team requested justification for the newly proposed regimen, which was provided the following month. The revised dosing regimen is based on post hoc analyses of completer patients in CS6-pivotal and a small group (n=15) of non-FCS patients in CS16-HTG; this regimen (for both dosing and platelet monitoring) was not evaluated prospectively in the phase 3 clinical program.

Efficacy Summary

CS6-pivotal was an international, randomized, placebo-controlled, 52-week trial comparing VLN 300 mg/week versus placebo in 66 adults with a clinical history and a genetic or biochemical profile intended to be consistent with FCS. Subjects were randomized 1:1 to VLN or placebo after an up to 8-week screening period for dietary stabilization. The primary endpoint was

[2] Pouwels ED, et al. "Severe hypertriglyceridaemia as a result of familial chylomicronemia: the Cape Town experience." *S Afr Med J* 2008;98:105-108.

percent change in fasting TG at Month 3.

Baseline characteristics were similar in the two treatment arms. Approximately 80% of subjects were white, the mean age was 46 years, 55% were women, and average BMI was 25 kg/m^2. Overall, 38% of patients were from North America, including 17% from the United States. Prior to the first dose, 49% of patients were receiving fibrates, 29% were receiving other lipid-modifying agents (e.g., fish oil derived products), and approximately 17% were receiving aspirin. Approximately 76% of patients had a history of pancreatitis, and 35% had at least one episode of pancreatitis in the 5 years before enrollment (per retrospective review and adjudication of medical records). Of the 66 patients enrolled in CS6-pivotal, 57 (86%) had genetic or functional testing (i.e. LPL activity) consistent with FCS. The other 9 patients did not have confirmatory testing: in 3 cases, the study geneticist did not concur with the genetic diagnosis of FCS (documented by medical history). The remainder either had issues with LPL activity testing procedures, which yielded an inaccurate result, or had on-study testing that did not corroborate a history of low LPL activity. These examples, which occurred in a clinical trial setting, underscore the potential complexities in identifying patients with FCS.

In CS6-pivotal, the treatment discontinuation rate was much higher in the VLN arm compared to the placebo arm; 14 (42%) of 33 subjects assigned to VLN discontinued study drug prematurely versus only 1 (3%) of 33 subjects assigned to placebo. Of the 19 VLN-treated patients that completed treatment, only 6 patients remained on weekly VLN dosing without dose interruption or elongation of the dosing interval. Dose adjustments were primarily due to adverse events, most commonly thrombocytopenia (see Safety Summary, below).

After a minimum 6-week diet stabilization in the screening period, the 66 CS6-pivotal patients had an average baseline TG of 2209 mg/dL (median 1985 mg/dL). Treatment with VLN 300 mg/week resulted in a statistically significant mean percent reduction in TG of 77% from baseline to Month 3 compared with an 18% increase on placebo. Statistically significant reductions in TG were maintained throughout the 52-week treatment period, although the magnitude of TG reduction was attenuated (33% reduction from baseline to Month 12 versus a 12% increase on placebo per the FDA analysis), most likely due to patient discontinuation and adjustment of VLN dosing. For the patients who completed CS6-pivotal with weekly VLN dosing, the degree of TG reduction was maintained at Month 12.

In planned secondary analyses of clinical endpoints, such as abdominal pain and acute pancreatitis, there were no significant differences between VLN and placebo. The applicant developed a patient-reported outcome (PRO) instrument to assess abdominal pain on a 0-10 numeric rating scale (NRS) and assessed the differences as a secondary endpoint. During the screening period, 74% of patients did not report any abdominal pain using this instrument weekly. During treatment, there was not a significant difference or a trend toward benefit for the prespecified secondary endpoint, average of maximum intensity of abdominal pain (means on placebo and VLN of 0.36 and 0.38, respectively,

p=0.9). Exploratory endpoints using the 36-item Short Form Health Survey version 2 (SF-36 v.2) and EuroQol Five Dimensions (EQ-5D) instruments, health status questionnaires routinely used in clinical trials, did not demonstrate any significant differences between VLN and placebo-treated patients or any consistent trends toward benefit.

Pancreatitis was an event of interest adjudicated by an independent committee. During the on-treatment period, 4 patients experienced 5 adjudicated pancreatitis events: 3 (9%) placebo-treated patients (4 events) and 1 (3%) VLN-treated patient (1 event). A comparison between groups was not statistically significant (p=0.6), and the FDA statistical reviewer hypothesized that more missing data in the VLN arm could account for the numerical difference favoring VLN. A pre-specified secondary analysis of the composite of adjudicated pancreatitis and patient-reported moderate-to-severe abdominal pain demonstrated no difference between treatment groups.

The applicant highlighted 2 unplanned (post hoc) analyses (one for abdominal pain, one for pancreatitis) – among over 150 tertiary, exploratory, and unplanned analyses – that purports to show statistically significant effects favoring VLN compared to placebo. These analyses are difficult to interpret due to multiple limitations, including very small sample sizes and lack of procedures to control Type 1 error. Similar analyses, using different variables (such as slightly different endpoint definitions, subgroup definitions, or prespecified imputation methods for missing data), did not demonstrate differences between treatment groups.

CS16-HTG was a 6-month randomized clinical trial in hypertriglyceridemic patients (TG≥500 mg/dL). Because it was not conducted in the population for which the applicant is seeking an indication, the efficacy results are not documented here in detail. Data from the study show that VLN lowered TG in this patient population to a degree comparable to the FCS population.

Safety Summary

CS6-pivotal was the primary trial to describe the safety of VLN in patients with FCS. The safety review was supplemented by CS7-OLE, an ongoing, open-label extension study in 60 (including 43 treatment-naïve) patients with FCS, and CS16-HTG, a 6-month, placebo-controlled trial in a non-FCS population [113 patients (75 VLN: 38 placebo)] with severe hypertriglyceridemia. Because of the differences in patient populations, treatment durations (1 year versus 26 weeks), and treatment allocation (1:1 randomization in CS6-pivotal versus 2:1 randomization in CS16-HTG), the studies were not pooled for the safety review. In general, the safety profile observed with VLN use in the pivotal trial (CS6-pivotal) was consistent with the safety data from the complementary studies.

Overall, in CS6-pivotal, individuals treated with VLN reported more treatment emergent adverse events (TEAEs) compared to their placebo-treated counterparts (985 TEAEs in 32/33 VLN patients and 227 TEAEs in 31/33 placebo patients). The most commonly

reported TEAEs in patients treated with VLN were injection site reactions. Excluding TEAEs at the injection site, events occurring among >10% of patients and with higher incidence in the VLN group include decreased platelet count, abdominal pain, fatigue, headache, nausea, vomiting, myalgia, arthralgia, petechiae, thrombocytopenia, epistaxis, and diabetes mellitus. Nine (27%) patients treated with VLN discontinued due to an adverse event versus no placebo treated patients.

The primary safety concern identified with VLN was thrombocytopenia and risk of bleeding. Other safety concerns include injection site reactions, hypersensitivity, immunogenicity, flu-like reactions, renal-related laboratory adverse events and elevations in liver enzymes.

- Thrombocytopenia and risk of serious bleeding: In CS6-pivotal, the average platelet count at baseline was 221,000/mm^3 (normal 140,000/mm^3 to 400,000/mm^3). Patients treated with VLN experienced a decline in mean platelet count of approximately 30% within the first 6 months compared to no significant change in the placebo arm. However, central tendency measures alone do not fully describe the clinically significant platelet reductions observed in the trial, as individual patients experienced unexpected, rapid, severe decreases in platelet count. In an analysis of individuals who reached a subnormal categorical nadir platelet count any time post baseline dose, a higher proportion of patients treated with VLN reached lower nadirs compared to patients treated with placebo in both CS6-pivotal and CS16-HTG. Although the applicant cited literature that suggests that patients with FCS may have significant variability in platelet counts, in CS6-pivotal no placebo-treated patient had a platelet count at any time post baseline below 100,000/mm^3 compared with 55% of patients treated with VLN.

  In the 1-year trial, CS6-pivotal, 3 (9%) of 33 patients treated with VLN had a platelet count <50,000/mm^3, including 2 patients with a platelet count <25,000/mm^3. In the entire development program – which includes 1 patient with FCS from the phase 2 trial, CS2, and one safety report submitted after the 4-month safety update – 9 patients had a platelet count <50,000/mm^3; the onset of was variable (range 51 to 300 days). Particularly notable was the fact that 4 of these events, including 2 patients with platelet nadirs of 15,000/mm^3 and 17,000/mm^3, occurred after implementation of enhanced platelet monitoring and dose adjustment.

  To date, no deaths or serious bleeding events have occurred in patients treated with VLN. However, using the Hemorrhage Standard MedDRA Query (SMQ), a higher proportion of VLN-treated patients in CS6-pivotal experienced bleeding events – 16 (49%) of 33 VLN-treated patients experienced 45 events versus 5 events in 4 (12%) of 33 placebo-treated patients. Excluding bleeding events at the injection site or lab-related event terms, the imbalance in bleeding persisted (36% VLN versus 6% placebo); the most common events were epistaxis and petechiae. No association with use of concomitant anti-platelet

medications and bleeding events was observed, although the numbers of patients taking these medications was small. Some of the clinical bleeding events occurred at platelet levels where spontaneous bleeding would be unexpected, suggesting possible platelet dysfunction. Evaluations for the underlying mechanism of VLN associated thrombocytopenia are, thus far, inconclusive.

- Injection-site reactions: In CS6-pivotal, 79% of VLN-treated patients experienced 497 injection site adverse reactions, compared to 0% of placebo-treated patients. Only 1 VLN-treated patient in CS6-pivotal reportedly discontinued due to local tolerability events at the injection site (with associated fatigue); for this patient discoloration and skin depression at the injection site persisted 4 months after the last dose of VLN. Higher percentages of injection site reactions were also observed in VLN-treated patients compared to placebo in CS16-HTG (87% VLN, 8% PBO). In Study CS6-pivotal, CS7-OLE, and CS16-HTG, skin discoloration at the injection site was noted in 20% to 30% of patients, which in several cases was persistent at the time of NDA submission.

- Hypersensitivity: Serious hypersensitivity reactions occurred in two non-FCS patients treated with VLN (one event of anaphylaxis requiring emergent treatment and one event of serum sickness requiring hospitalization and steroids). The onset of symptoms of serum sickness was coincident with the emergence of high titers of anti-VLN antibodies (ADA). Both patients recovered with discontinuation of VLN and supportive care. No serious hypersensitivity events have occurred in the FCS population, although one patient developed itching and erythema involving the whole body surface, leading to treatment with steroids, antihistamines, and eventually cyclosporine.

- Immunogenicity: Of the 33 VLN-treated patients in CS6-pivotal, 11 (33%) patients tested positive for ADA. The median time of onset was approximately 6 months. It did not appear that changes in ADA titers correlated with an impact on TG levels or platelet counts. Two patients with FCS discontinued VLN treatment due to systemic symptoms of chills and sweating or chills, fever, myalgias (1 in CS6-pivotal, 1 in CS7-OLE). Both patients were positive for ADA at the time symptoms were reported. The contribution of ADA to these events and the case of serum sickness cannot be definitively ruled out.

- Flu-like reactions: VLN treatment was associated with flu-like reactions, other constitutional symptoms, and increases in the inflammation biomarker hsCRP. Two (6%) VLN-treated patients discontinued treatment due to fatigue in CS6-pivotal and one patient in CS7-OLE; there were also higher proportions of VLN-treated patients (≥8%) reporting constitutional symptoms such as fatigue, myalgia, arthralgia, diarrhea, nausea, and abdominal pain as an AE compared to placebo-treated patients in both CS6-pivotal and CS16-HTG.

- Renal-related adverse events: Small imbalances in renal-related events were noted in CS6-pivotal with VLN treatment – transient increase in creatinine (50% increase from baseline

or ≥0.3 mg/dL) was observed in 4 (12%) VLN patients compared to no such changes in placebo-treated patients. No serious renal events were reported. However, given the small safety database and the association of renal adverse events (e.g. glomerulonephritis) with other antisense oligonucleotides, routine monitoring for these types of events may be warranted.

- Elevated liver enzymes: Two non-FCS patients treated with VLN in CS16-HTG met liver-related stopping criteria for elevated ALT and AST values >8x ULN. One case was confounded by alternative etiologies. In the other case, following 4 doses of VLN treatment, liver enzymes were >8xULN, the patient's bilirubin remained normal, no alternative etiology could be discerned, and liver enzymes normalized with study drug discontinuation. Given the temporal association with VLN-treatment, a causal association cannot be excluded. No patient treated with VLN met the laboratory criteria for Hy's law (i.e., ALT or AST greater than 3x ULN accompanied by total bilirubin greater than 2x ULN).

Conclusion

FCS is a rare monogenic disorder of lipid metabolism characterized by excessive chylomicronemia and very severe hypertriglyceridemia. The most serious clinical consequence of this disorder is recurrent pancreatitis, which can be life-threatening. Patients living with FCS can experience other symptoms that may be severe and debilitating. There is currently no approved product indicated for patients with FCS. The treatment armamentarium would benefit from an effective and safe treatment option for this patient population.

It is important to ensure that the appropriate patient population is targeted, given the serious risks that may be associated with VLN therapy. Considering that the onset of clinical symptoms frequently occurs in childhood, the potential for off-label use in a pediatric population is significant and it is concerning, especially if frequent laboratory monitoring is required for safe use.

The lipid biomarker TG has historically been used as a surrogate for reduction in risk of pancreatitis and the basis of approval for TG-lowering drugs in patients with severe hypertriglyceridemia (TG ≥500 mg/dL). The effect of VLN on TG levels is compelling given the minimal effect of other TG-lowering drugs in patients with FCS. However, the magnitude of clinical benefit with VLN treatment in patients living with FCS is uncertain. There was no evidence of an effect on abdominal pain or other PROs in the phase 3 trial, and there were too few pancreatitis events to reliably evaluate the effect on pancreatitis risk; however, the trial was not powered to detect these effects. The benefit of TG lowering in this population with severely elevated TG levels must be weighed against the risks observed with VLN treatment.

The primary safety concern is thrombocytopenia and risk of serious bleeding. The data are not adequate to identify which patients are at risk for experiencing a precipitous drop in platelet count, and the timing of onset is highly variable. The lack of predictability and the seriousness of this safety issue is illustrated by the fact that in a clinical trial with structured oversight, strict

monitoring, and dosing rules, two subjects experienced severe thrombocytopenia with platelet nadirs less than 25,000/mm^3, including one who was being monitored with weekly platelet counts.

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/monitoring may be reasonable, but it has not been systematically evaluated, and it is not yet clear that it would substantially improve the safety profile for use of VLN in this patient population. Although a decision on the approvability of VLN has not been made at this time, discussions regarding Risk Evaluation and Mitigation Strategy (REMS) options for this product have occurred in parallel with the clinical review and will be discussed. 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 VLN, considering the data that are available at this time.

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1. Introduction

1.1. Product Introduction

Volanesorsen (Waylivra) is a 2'-O-(2-methoxyethyl) antisense oligonucleotide (ASO) inhibitor of the molecular target apolipoprotein C-III (apoCIII). Volanesorsen (VLN) is delivered as a subcutaneous injection of 300 mg/1.5 mL weekly in a single-use pre-filled syringe. The applicant (Akcea Therapeutics, an affiliate of Ionis Pharmaceuticals) has submitted this New Drug Application (NDA) to support the following treatment indication:

Waylivra is indicated as an adjunct to diet for the treatment of patients with familial chylomicronemia syndrome.

VLN is a second-generation synthetic oligomer of 20 nucleotides connected sequentially by a phosphorothioate backbone and flanked by two 2'-O-(2-methoxyethyl) (MOE)-modified ribonucleotides. The structure confers increased stability and affinity but does not prevent degradation by RNase H1 enzymes. VLN is complementary to a region of the apoC-III mRNA transcript.

ApoC-III is a 79-amino acid glycoprotein that is synthesized in the liver. ApoC-III resides primarily on apoB lipoproteins (chylomicrons and VLDL) and to a lesser degree on HDL. Apo C-III plays a critical role in the regulation of triglyceride (TG) levels via its inhibition of lipoprotein lipase (LPL)-mediated hydrolysis of TG and interference with the liver's uptake of TG remnants. VLN binds to its target and causes RNase H1-mediated degradation of apoC-III mRNA, inhibiting translation of the protein. By inhibiting apoC-III production, TG levels should decrease.

2. Therapeutic Context

2.1. Analysis of Condition

Familial Chylomicronemia Syndrome (FCS), also known as Type I hyperlipoproteinemia, is a rare, autosomal recessive disease characterized by persistent marked elevations in chylomicrons and triglycerides due to reduced or absent lipoprotein lipase activity. According to the applicant and literature sources, the prevalence is estimated to be 1 to 2 in 1,000,000, or approximately 300 to

600 individuals in the United States.[3] The most common form of FCS is familial LPL deficiency (i.e., biallelic pathogenic variants in the *LPL* gene), with biallelic pathogenic variants in other genes being far less common (e.g., *APOC2*, *GPIHBP1*, *APOA5*, and *LMF1,* discussed below).[4]

In very simple terms, the pathogenesis of FCS is a result of an imbalance in factors regulating TG metabolism. Triglycerides are primarily carried in the body via the lipoproteins VLDL and chylomicrons. VLDL particles transport endogenous triglyceride produced in the liver, and chylomicrons transport triglycerides derived from dietary fat. LPL is a key enzyme that catalyzes the hydrolysis of TG from VLDL and chylomicrons into free fatty acids for use in muscle and adipose tissue, and it plays a major role in maintaining normal TG levels in plasma. LPL is produced in muscle, heart, and adipose tissue, and the enzyme is transported to its site of action, the capillary endothelium. Normal LPL function depends on 4 cofactors critical for its maturation, secretion, stabilization, and action: lipase maturation factor 1 (LMF1, involved in maturation process of LPL), glycosylphosphatidylinositol-anchored high-density lipoprotein–binding protein 1 (GPIHBP1, anchoring protein of LPL), apoA5 (stabilizes lipoprotein/enzyme complex), and apoC-II (a LPL coactivator) (Figure 1). Other critical proteins regulating TG include apolipoprotein C-III, which is the target of VLN. ApoC-III inhibits LPL, thereby counteracting the ability of LPL to lower TG levels; furthermore, apoC-III interferes with TG uptake by hepatic receptors, also promoting a more TG-rich plasma.[5] This is a simplistic summary of a complex process that involves several other enzymes, proteins, and receptors that are beyond the scope and purpose of this review.

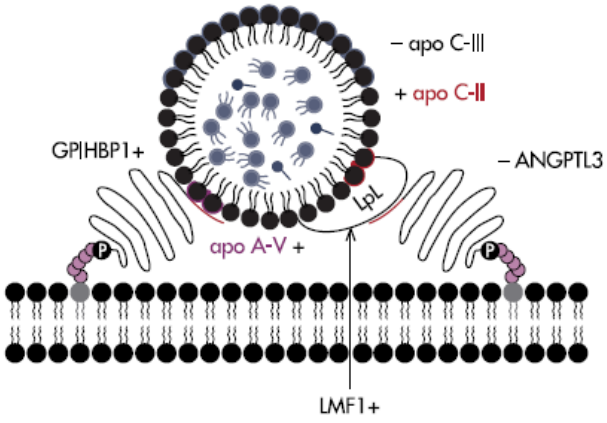


Figure 1. Schematic of proteins involved in lipolysis of TG rich lipoprotein

A plus sign indicates enhancement or stimulation of LPL-mediated lipolysis, minus sign indicates inhibition.
Source: Lewis 2015

More than 100 pathogenic variants in the *LPL* gene have been described; individuals with FCS may be homozygotes (same mutation in both alleles) or carry two different mutations (compound

[3] Gotoda T et al. Diagnosis and Management of Type I and Type V Hyperlipoproteinemia. J Atheroscler Thromb. 2012;19:1-12
[4] Burnett JR, Hooper AJ, and RA Hegele. "Familial Lipoprotein Lipase Deficiency." Gene Reviews. Updated June 22, 2017. https://www.ncbi.nlm.nih.gov/books/NBK1308/
[5] Gordts PL et al. ApoC-III inhibits clearance of triglyceride-rich lipoproteins through LDL family receptors. J Clin Invest 2016;126(8):2855-66

heterozygotes) in each *LPL* allele. There are also small numbers of families reported in the literature with rare pathogenic mutations associated with the 4 cofactors mentioned previously.

The diagnosis of FCS may not always be straightforward. For example, heterozygous carriers of defective alleles in the genes referenced above may be predisposed to severe hypertriglyceridemia, especially when accompanied by secondary factors such as diabetes, obesity, pregnancy, or other genetic dyslipidemic variants.[6,7] Thus, the prevalence of conditions that could clinically resemble FCS likely far exceeds 1-2 per million – perhaps as high as 1:600 (Table 1). As will be discussed later in this review, there is evidence from the trials conducted in the VLN development program that the diagnosis of FCS can be challenging. Given that there are serious safety concerns related to VLN treatment, the ability to identify a patient population for whom benefit could be expected to exceed risk is a critical consideration, both for a regulatory decision and as a guide to individual physicians making prescribing decisions, if approved.

Table 1. Features of monogenic and polygenic chylomicronemia

Features	Monogenic chylomicronaemia	Polygenic chylomicronaemia
Former designations	Familial chylomicronaemia Type 1 hyperlipoproteinaemia (WHO)[2]	Mixed dyslipidaemia Type 5 hyperlipoproteinaemia[2] (WHO)
Main lipoprotein disturbances	Increased number of chylomicron particles only[5,11]	Transient increase in levels of triglyceride-rich lipoproteins Increased number of chylomicron particles Increased levels of VLDL Increased number of chylomicron remnants Increased number of VLDL remnants[4]
Associated lipoprotein disturbances	Reduced levels of VLDL, LDL and HDL	Usually reduced levels of HDL, sometimes reduced levels of LDL
Typical onset	Paediatric or adolescent	Adulthood
Clinical features	Failure to thrive Abdominal pain Nausea Vomiting Eruptive xanthomas Lipaemia retinalis Pancreatitis Hepatosplenomegaly[5]	Abdominal pain Nausea Vomiting Eruptive xanthomas (rare) Lipaemia retinalis (rare) Pancreatitis (~1% risk per year)[4]
Association with CVD	Minimal	Some evidence of increased risk[25,63]
Prevalence	~1:100,000 to ~1:1,000,000[4]	~1:600[6]
Contribution of secondary factors	Minimal	Major
Inheritence pattern	Autosomal recessive	Familial clustering, but no discrete classical pattern
Genetic causes	Mutations in *LPL*,[4] *APOC2*,[4] *APOA5*,[43] *GPIHBP1*[51] and *LMF1*[55]	Genetic pool of affected individuals has increased prevalence of: ▪ Heterozygous rare variants in *LPL*, *APOC2*, *APOB*, *GCKR*, *APOA5*, *LMF1*, *GPIHBP1* and *CREBH* with large effects[60,61] ▪ Common variants (SNP) with small effects in ~40 genes identified in genome-wide association studies[60]
Current treatment	Dietary control: restriction of fat intake ± increased consumption of MCTG Pharmacologic control: minimal effect of fibrates, niacin, ω-3 fatty acids and statins	Dietary control: reduced intake of calories, fats, simple sugars and alcohol Control of secondary factors Pharmacologic control: ω-3 fatty acids and niacin (both have variable efficacy)

Abbreviations: CVD, cardiovascular disease; MCTG, medium chain triglyceride; SNP, single nucleotide polymorphisms.

[6] Rabacchi C et al. Spectrum of mutations of the LPL gene identified in Italy in patients with severe hypertriglyceridemia. Atherosclerosis;2015:79-86

[7] Lewis GF et al. Hypertriglyceridemia in the genomic era: a new paradigm. Endocrine Reviews;2015:131-47

Source: Brahm & Hegele 2015

The classic presentation of FCS is characterized by symptom onset usually in childhood or adolescence. Common signs and symptoms in this population include episodic abdominal pain, eruptive xanthomas, and hepatosplenomegaly. Additional reported symptoms include lack of appetite, generalized weakness, and fatigue.[8] Cognitive and psychosocial symptoms include difficulty concentrating, "brain fog," memory loss, anxiety, and depression.

The most serious complication of FCS is recurrent pancreatitis. The severity of acute pancreatitis ranges from relatively mild, self-limiting episodes to life-threatening events. Risk of pancreatitis increases as TG levels rise; TG thresholds quoted as associated with greater risk of pancreatitis vary and include >880 mg/dL and >1000 mg/dL; however, TG-lowering therapy to prevent acute pancreatitis is recommended for TG >500 mg/dL.[9,10,11] The overall mortality rate for an event of acute pancreatitis is approximately 5%, but may be even higher in the subset of patients with more severe pancreatitis complications such as organ failure or pancreatic necrosis.[12,13] However, not all patients with FCS experience acute pancreatitis; estimates of the lifetime incidence of pancreatitis in this population range from approximately 50 to 80%.[14] The rate of pancreatitis events in the FCS population has been estimated at 0.2 to 0.35 episodes per patient-year.[15]

Although symptom onset usually occurs in childhood or adolescence, diagnosis may be delayed given the rarity of the condition and varying degrees of clinical presentation. A diagnosis of FCS is *suspected* based on clinical characteristics of lipemic blood in the fasted state, elevated TG, and one or more of the following: a history of acute pancreatitis (as adult or child) or recurrent abdominal pain without definable cause, eruptive cutaneous xanthoma, or hepatosplenomegaly. More common risk factors for hypertriglyceridemia (such as diabetes mellitus, obesity, and excessive alcohol use) should be excluded. Regarding the TG level to suspect FCS, various thresholds have been suggested, including >750 mg/dL (chosen by

[8] Davidson et al. The burden of familial chylomicronemia syndrome: interim results from the IN-FOCUS study. Expert Rev Cardiovasc Ther. 2017;15(5):415-23
[9] Catapano AL et al. ESC/EAS Guidelines for the management of dyslipidemias. Atherosclerosis. 2011;217(1)3-46
[10] Berglund L et al. Endocrine Society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2012;97(9):2969-2989
[11] NCEP ATP III. Third report of the NCEP expert panel on detection, evaluation, and treatment of high blood cholesterol in adults final report. Circulation. 2002;106(25):3143-3421
[12] Scherer J et al. Issues in hypertriglyceridemic pancreatitis: an update. J Clin Gastroenterol 2014;48:195-203
[13] Koutroumpakis E et al. Management and outcomes of acute pancreatitis patients over the last decade: A US tertiary-center experience. Pancreatology;2017:32-40
[14] Stroes et al. Diagnostic algorithm for familial chylomicronemia syndrome. Atherosclerosis Supplements 23;2017:1-7
[15] Protocol CS7-OLE, Table 4 Expected Event for Protocol Defined Population (references Gaudet et al 2010, 2013)

applicant), >1000 mg/dL (Miller et al [16]), >2000 mg/dL (Brunzell[17]), and >880 mg/dL (Brahm and Hegele[18]). Diagnosis is confirmed by molecular genetic testing and, in some specialized centers, by the detection of low or absent LPL enzyme activity. The FDA has not approved tests for LPL enzyme activity or for the genetic diagnosis of this condition.

One diagnostic algorithm proposed for FCS is presented in Figure 2. In this algorithm, once a patient is suspected to be affected by FCS, genetic analysis is proposed as a "fundamental step to establish a correct diagnosis." The final step in diagnosing an individual with FCS is further analysis to determine pathogenicity of novel variants detected.

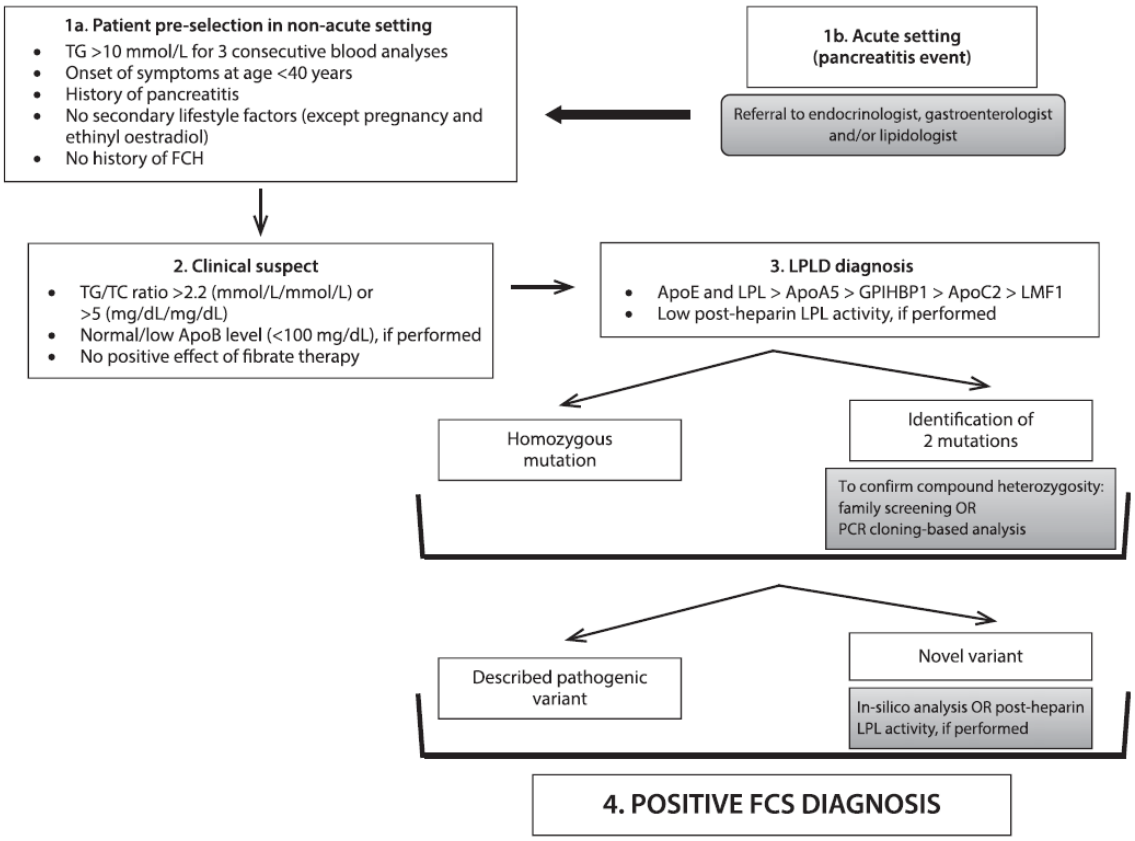


Figure 2. Proposed algorithm for diagnosis of familial chylomicronemia syndrome
Source: Adapted from Stroes et al [19]

[16] Miller et al. Triglycerides and cardiovascular disease: A scientific statement from the American Heart Association. Circulation 2011;123:2292-2333
[17] Brunzell JD. Familial Lipoprotein Lipase Deficiency. Gene Reviews. 1999-2011
[18] Brahm AJ, Hegele RA. Chylomicronemia-current diagnosis and future therapies. Nat. Rev. Endocrinol. 2015
[19] Stroes E et al. Diagnostic algorithm for familial chylomicronemia syndrome. Atherosclerosis Supplements 2017; 23:1-7.

2.2. Analysis of Current Treatment Options

There are no FDA-approved medications for the treatment of FCS. Classes of medications that are approved for the treatment of severe hypertriglyceridemia (TG≥500 mg/dL) related to other dyslipidemic conditions include fibrates, prescription fish oil derivatives, niacin, and statins. These medications are largely ineffective in lowering TG among patients with FCS. Effective and safe treatment options for patients with FCS are needed.

2.3. Important Safety Issues With Consideration to Related Drugs

The table below lists recent oligonucleotide therapies that have been reviewed by the FDA or are currently under review.

Hematologic effects have been noted to varying degrees in the labels of at least 3 of these products. Inotersen, an anti-sense oligonucleotide, is under review for the treatment of hereditary transthyretin amyloidosis. Complications of severe thrombocytopenia, including a fatal intracranial hemorrhage, have been observed in its clinical development program.[20]

Table 2. FDA-approved/reviewed/under review oligonucleotide therapies

Drug	Indication	Approved	Risk
Kynamro (mipomersen)	Homozygous familial hypercholesterolemia	2013	REMS for hepatotoxicity (box warning) In the phase 3 trial in patients with HoFH, the mean change in platelet count from baseline to Week 28/Early Termination was -30.6 × 10 /µL in the mipomersen group and +8.1 × 10 /µL in the placebo group. Idiopathic thrombocytopenic purpura in post-marketing
Exondys-51 (eteplirsen)	Duchenne muscular dystrophy	2016	Hypersensitivity reactions Contusion
Spinraza (nusinersen)	Spinal muscular dystrophy (intrathecal administration)	2016	Hematological effects (coagulation abnormalities, incl thrombocytopenia) -11% developed platelet count less than lower limit of normal. No platelet count <50,000/mm^3; Renal toxicity
Inotersen	Hereditary transthyretin amyloidosis	Under review[21]	Thrombocytopenia; fatality from intracranial hemorrhage (b) (4)

[20] https://www.prnewswire.com/news-releases/ionis-pharmaceuticals-announces-phase-3-neuro-ttr-study-of-inotersen-ionis-ttr-rx-meets-both-primary-endpoints-300457281.html
[21] http://ir.ionispharma.com/news-releases/news-release-details/ionis-announces-submission-new-drug-application-nda-inotersen-us

Drug	Indication	Approved	Risk
Drisapersen	Duchenne Muscular Dystrophy	Not Approved[22]	Severe thrombocytopenia – 6 patients (2%) with platelet count <20,000/mm^3 in uncontrolled extension study after 14-26 months of drisapersen treatment. Despite routine monitoring of platelets every 2 weeks, thrombocytopenia occurred precipitously[23]

3. Regulatory Background

3.1. Summary of Presubmission/Submission Regulatory Activity

IND 115063 for VLN was submitted in May 2012 after one phase 1 study had been completed and another dose-ranging study was ongoing outside of the United States. In November 2013, the IND was placed on partial clinical hold (PCH) due to adverse morphologic changes to the hearts of mice and rats, and cardiac-related deaths in mice at clinically relevant doses. Dose limits were instituted for ongoing and future clinical trials until the PCH was removed in January 2014 after FDA reviewed additional nonclinical data, including a 9-month monkey study that did not show pathogenic changes in heart structure (at doses up to 13-14x the proposed maximum human VLN dose, 300 mg/week).[24]

At the End-of-Phase 2 (EOP2) Meeting on April 10, 2014, major topics of discussion included the patient population, the adequacy of the safety database, the appropriateness of the dose, and the selection of endpoints for Phase 3 trials. The Division advised the applicant to recruit patients that would be representative of the target population with FCS. For example, the applicant proposed to exclude patients with platelet counts less than the lower limit of normal from the pivotal trial, despite describing thrombocytopenia as not an uncommon occurrence in patients with FCS. The Division also recommended enriching the patient population with patients with a history of hypertriglyceridemia-associated pancreatitis.

At the EOP2 meeting, the Division asked if the applicant planned to study VLN pediatric patients given that FCS often presents early in childhood or adolescence. The applicant stated they planned to conduct a separate small study in pediatric patients.

[22] https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0ahUKEwjDpfvEgKHaAhWLUt8KHV4UBnsQFggpMAA&url=http%3A%2F%2Finvestors.biomarin.com%2F2016-01-14-FDA-Issues-Complete-Response-Letter-for-KyndrisaTM-for-Duchenne-Muscular-Dystrophy-Amenable-to-Exon-51-Skipping%3FasPDF&usg=AOvVaw2SRyUIbjkjQD9WmGuwB9cF

[23] https://wayback.archive-it.org/7993/20170403224050/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystemDrugsAdvisoryCommittee/ucm467181.htm

[24] Elmore CL. Review of Response to Partial Clinical Hold 17 January 2014

The applicant asked if a statistically significant decrease in fasting TG would be acceptable to support approval of VLN as an adjunct to diet to reduce TG levels in adult patients with FCS. The Division responded that although a primary efficacy endpoint of reducing fasting TG is reasonable, "a statistically significant reduction in triglycerides alone might not provide a sufficient basis for approval in this population. To our knowledge, it is unknown to what extent reducing extremely high levels of triglycerides affects clinical outcomes when the on-treatment levels remain extremely high." The Division strongly recommended assessing other outcomes that were meaningful (i.e. that evaluate how a patient feels or functions) to patients with FCS. The Division acknowledged that although a trial would be underpowered to show a reduction in clinical outcomes such as pancreatitis, the "totality of the data would be used in our risk/benefit assessment during review." The applicant stated that they planned to incorporate quality of life questionnaires, adjudicate pancreatitis events, and assess other symptoms such as abdominal pain and xanthoma to more fully inform the meaningfulness of TG lowering.[25]

The size of the safety database at the time of the EOP2 meeting was approximately 100 patients exposed to any dose of VLN, 74 subjects in two 13-week phase 2 studies and 25 subjects with single or multiple (6) doses of VLN from 50 to 400 mg. Only 38 patients (3 with FCS) had been exposed to VLN 300 mg/week in 3-month duration trials at that time. The Division expressed concern that the development program was "extremely limited, with very little experience with your planned dose of 300 mg/week." The Division encouraged the applicant to increase the safety database, adding "if you proceed with efficacy defined by changes in a biomarker, it would be to your advantage to have a well-defined safety profile to maximize the probability of a favorable benefit/risk assessment." The Division further stated that, "We believe that you are taking a substantial risk to proceed into phase 3, especially when targeting a rare disease, with such a small phase 2 clinical database" and questioned the applicant's characterization of safety and tolerability in light of the limited patient exposure to VLN. The Division noted that the applicant was planning a program for severe hypertriglyceridemia and suggested this population could provide supportive data for the FCS population. Last, the Division encouraged the applicant to study more dosing regimens than only 300 mg weekly in the phase 3 program, in case this regimen proved less safe/tolerable than they anticipated.

Ultimately, the applicant elected to design a 52-week, placebo-controlled trial ("CS6") to study volanesorsen in ~50 patients with FCS followed by an open-label extension ("CS7"). In addition, to characterize better the safety profile of VLN and support approval of VLN for FCS, the applicant designed a 6-month, placebo-controlled trial ("CS16") in 75 patients with severe hypertriglyceridemia (fasting TG ≥500 mg/dL). The Division encouraged the applicant to increase the size of the safety database further; in response, the applicant increased the sample size in CS16 from 75 to 105 patients.

The Division involved the Clinical Outcomes Assessment staff in the review of phase 3 protocols given the anticipation that effects on endpoints that reflect how patients feel or function may

[25] IND 115063, EOP2 meeting minutes, 7 May 2014

be important in the benefit/risk assessment. Several comments regarding the PRO for abdominal pain were included in a January 29, 2015, advice letter. For example, it was noted that abdominal pain should be sufficiently high at study baseline to increase the ability to demonstrate improvement over the course of the trial. The Division also recommended conducting cognitive interviews to ensure patients understood the PRO.

On April 26, 2016, the Division sent the applicant an information request to evaluate the risk of thrombocytopenia and related safety monitoring of VLN after a fatal intracranial hemorrhage related to thrombocytopenia was reported in another anti-sense oligonucleotide development program. A response to the Division's request was submitted on May 10, 2016. During the review of the response, on May 31, 2016, two 15-day safety reports were submitted describing serious adverse events of thrombocytopenia requiring hospitalization and pharmacologic intervention. In response, the applicant submitted several protocol amendments, including modifications to platelet monitoring and dosing strategies, while the phase 3 trials were underway, leading to temporal heterogeneity in how patients were treated and monitored in the phase 3 program. This will be described in further detail in the relevant sections of this review.

On July 13, 2016, the applicant amended the open-label CS7 to allow patients with FCS to enroll even if they had not participated in either the pivotal FCS trial, CS6 (hereafter "CS6-pivotal") or the severe HTG trial, CS16 (hereafter "CS16-HTG"). It was anticipated that 10 new patients with FCS would qualify for enrollment in CS7. Given that the applicant was identifying new patients with FCS and that there were outstanding questions regarding VLN dosing and the risk for thrombocytopenia, the Division responded on July 25, 2016, encouraging the applicant to enroll a second adequate and well-controlled trial to gather data that would be more helpful in characterizing the benefit/risk of the drug than additional open-label data.

Despite the applicant's institution of "enhanced platelet monitoring," a 15-day safety report describing a patient with severe thrombocytopenia (platelet count <25,000/mm^3) treated with VLN in the open-label study was received on February 15, 2017. Nine days later, the Division sent recommendations for additional platelet monitoring and investigations (such as bone marrow biopsies and platelet function testing) as well as the following comment:

"You continue to incorporate modification of the dosing regimen (150 mg weekly or 300 mg every 2 weeks, without any apparent rationale for choosing one over the other) as part of your safety measures, and we note that your safety monitoring and dose adjustment requirements are being modified after the last patient has received the last dose of drug in your FCS pivotal trial (study CS6). Your proposal to adjust dosing to regimens other than 300 mg weekly suggests that you believe that the effect of volanesorsen on platelets may be dose- and/or exposure-dependent. However, it does not appear that your program is designed to characterize the safety and effectiveness of these alternative regimens. We strongly advise you, therefore, to consider how you might address this concern in your drug development program."

The applicant agreed to incorporate the Division's safety recommendations, including weekly measurement and review of platelet counts prior to dosing for all patients and permanent

discontinuation of study drug and referral to a hematologist, for platelet values <50,000/mm^3. Regarding the Division's recommendation for platelet function testing, the applicant acknowledged that no platelet function testing in VLN-treated patients had been done, and stated that they were considering incorporating this into the ongoing open-label CS7. The applicant did not address the Division's recommendation to consider further exploration of the safety and effectiveness of an alternative dosing regimen with VLN in newly identified patients with FCS naïve to treatment with VLN.

On March 28, 2017, the applicant requested a pre-NDA meeting for VLN for treatment of FCS. The pre-NDA meeting was held on June 14, 2017, with additional clarifying information submitted to the Division on July 25, 2017.

The applicant submitted the NDA on August 30, 2017.

3.2. Clinical Pharmacology

The dose-finding phase 2 study (also referred to as CS2-DF in this document), demonstrated dose-dependent reductions in both apoC-III protein and TG when VLN was administered at doses of 100, 200, and 300 mg weekly for 13 weeks in patients with hypertriglyceridemia (≥225 mg/dL if on fibrate, ≥440 mg/dL if not on TG-lowering therapy). The steady state triglyceride reduction appeared to be reached at approximately Week 9. At the end of Month 3, mean serum triglyceride percent change from baseline was 20.1% (increase) in the placebo arm, compared to -31.3%, -57.7%, and -70.9% following 100 mg/wk, 200 mg/wk, and 300 mg/wk VLN, respectively.

The reader is referred to the clinical pharmacology review team's assessment of VLN for further analysis of dose selection and the proposed revision to the dosing regimen.

4. Sources of Clinical Data and Review Strategy

4.1. Table of Clinical Studies

The following table lists the studies submitted to the NDA pertinent to the evaluation of efficacy and safety of VLN.

Table 3. Listing of Clinical Trials Relevant to the EMDAC Meeting

Trial Identity (NCS no.)	Study Population	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. of patients enrolled	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety					
CS6 (02211209)	Adults with FCS	Phase 3 R, DB, PC 52-week study Pts randomized 1:1 VLN vs. PBO	300 mg/wk PBO SC	TG	52 wks	67	40 centers 11 countries
		Studies to Support Safety					
CS16 (02300233)	Adults with severe HTG	Phase 3 R, DB PC 26-week study Pts randomized 2:1 VLN vs. PBO	300 mg/wk PBO SC	TG	26 wks	114	35 centers 6 countries
CS7 (02658175)	Adults with FCS	OLE study of study CS6	300 mg/wk SC	TG	52 wks	29 (at data cutoff) 60 (at 4-month safety update-cumulative)	19 centers 10 countries
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)					
CS2 (01529424)	Adults with severe or uncontrolled HTG	Phase 2 R, DB, PC, dose response study Pts randomized equally to 4 treatment arms	100 mg/wk 200 mg/wk 300 mg/wk PBO/wk SC	TG	13 wks	88	8 centers 2 countries

MXF: Moxifloxacin; VLN: Volanesorsen; R: Randomized, DB: Double-blind, PC: Placebo controlled, OLE: Open-label extension, HTG: Hypertriglyceridemia

4.2. Review Strategy

The primary focus of this review, given the applicant's proposed treatment indication, is the single pivotal FCS trial, referred to in this document as CS6-pivotal. Supportive safety data for the FCS population comes primarily from 2 sources: (1) Study CS7, an ongoing open-label extension study (referred to as CS7-OLE) that allows up to 104 weeks of treatment following CS6-pivotal, and (2) the 26-week, placebo-controlled trial referred to as CS16-HTG, in which 113 patients with severe hypertriglyceridemia (TG ≥500 mg/dL) were assigned to either VLN 300 mg/week or placebo; this trial was complete at the time of NDA submission.

Only patients with FCS could participate in CS7-OLE. The CS7-OLE population comprised patients who had completed either of the parent studies CS6-pivotal or CS16-HTG (which enrolled of 7 patients with FCS because CS6-pivotal enrollment had closed) as well as patients with FCS who had not participated in either parent study. The combination of these "new" patients as well as those who had only received placebo in parent trials forms a "treatment-naïve" group that received their first exposure to VLN in study CS7-OLE.

The datasets for CS6-pivotal and CS16-HTG were essentially complete at the time of NDA submission (except for a small amount of off-treatment follow-up data from CS6-pivotal). At the time of initial data cut-off for CS7-OLE (6 January 2017), 29 patients had enrolled and were included in the initial submission. The 4-month safety update, which used a data cut-off of 31 August 2017, included a cumulative total of 60 patients from this open-label study because the applicant continued to enroll new, treatment-naïve patients with FCS.

5. Review of Efficacy

Summary of Efficacy

The efficacy of VLN in patients with FCS relies on a single trial, CS6-pivotal. The strengths of this trial include the use of a placebo-control, the length of treatment duration, the adjudication of pancreatitis events, and use of a patient-reported outcome (PRO) measure of abdominal pain. Limitations of this trial include the use of a PRO that was not validated, absence of systematic collection of other FCS disease-specific outcomes that may be clinically meaningful to patients living with FCS, and the high rates of treatment discontinuation and dose adjustment with VLN.

The efficacy of VLN in this patient population is summarized here.

- At the primary efficacy endpoint (Month 3), treatment with VLN significantly reduced TG by 77% from baseline compared to an 18% increase for placebo ($p<0.0001$).
- The magnitude of TG lowering was attenuated over time, most likely due to treatment discontinuation or dose adjustments. The FDA statistical reviewer estimated that

treatment with VLN reduced TG 33% from baseline to Month 12 compared to a 12% increase for placebo, using a multiple imputation model for missing data; this treatment difference was statistically significant.
- In the applicant's analysis of the effect of dose interval change or dose pauses in patients that completed CS6-pivotal, TG decreased from baseline by 54% at Month 12 in the 13 VLN-treated patients that completed the study with a dose adjustment compared to a 76% reduction in the 6 VLN-treated patients that maintained weekly VLN 300 mg for 52 weeks.

The effect of VLN on TG reductions is compelling given the minimal effect of other TG-lowering medications in patients with FCS, and FDA has approved medications on the basis of lowering TG in patients with severe hypertriglyceridemia (TG ≥500 mg/dL). Basing approval on an effect on a surrogate endpoint, however, almost always leaves uncertainty with respect to the magnitude of the clinical benefit to patients (e.g., the absolute risk reduction of pancreatitis). Especially when a drug carries one or more serious risks, this uncertainty with respect to the magnitude of benefit can lead to a challenging benefit/risk assessment; therefore, it could be helpful if a favorable effect were observed on other clinically relevant endpoints to patients. In the VLN development program, the following results from planned secondary analyses of clinical endpoints were observed:

- During the treatment period, no difference was detected between VLN-treated and placebo-treated patients in the average of maximum intensity of patient-reported abdominal pain (means on placebo and VLN of 0.36 and 0.38, respectively, on a 0-10 scale assessed weekly; p=0.9). Of note, 74% of patients did not report any abdominal pain during the 6-week screening period, and 56% did not report any abdominal pain during the trial.
- During the treatment period, no difference was detected between VLN-treated and placebo-treated patients in the composite of pancreatitis and moderate to severe abdominal pain (means on placebo and VLN of 2.04 and 2.73 events per year, respectively, p=0.6).

It should be noted that CS6-pivotal was neither optimally designed nor powered to detect differences on these endpoints; therefore, these results should not be interpreted as evidence against lowering TG as a means to reduce the risk of pancreatitis. Nevertheless, these analyses do not provide evidence that helps characterize the magnitude of clinical benefit to weigh against the risks of VLN, either.

Planned exploratory analyses of clinical endpoints (not included in the multiple testing hierarchy to control Type 1 error) also did not demonstrate clinical benefit for VLN:
- No FCS-specific PRO assessments were measured; no differences were observed in general quality of life questionnaires, SF-36 v2, EQ-5D.
- In the pivotal trial, 3 placebo-treated patients experienced 4 adjudicated pancreatitis events on-treatment (last dose + 28 days) compared with 1 VLN-treated patient who

experienced 1 event (p=0.6). The FDA statistical reviewer hypothesized that more missing data in the VLN arm could account for the numerical difference favoring VLN.

The applicant highlighted two unplanned (post hoc) analyses suggesting clinical benefit for VLN: an analysis of abdominal pain among the subset of 17 patients who reported any abdominal pain during the screening period, and an analysis of adjudicated pancreatitis events in the subset of 11 patients with at least 2 prior events of pancreatitis in the five years prior to enrollment. Both analyses are difficult to interpret due to multiple limitations, including very small sample sizes and lack of procedures to control Type 1 error. Similar planned (prespecified) analyses using different variables, such as slightly different endpoint definitions (e.g. worst maximum pain intensity versus average maximum pain intensity), or imputation methods for missing data (next observation carried backward versus imputation of zero for missing values) did not demonstrate treatment differences.

Overall in patients with FCS, treatment with VLN did not significantly reduce the frequency and severity of abdominal pain compared with placebo treatment. Systematic collection of data regarding other potential clinically meaningful outcomes specific for this patient population was not done.

5.1. Study CS6-pivotal FCS trial

5.1.1. Study Design

Overview and Objective

Study CS6-pivotal was conducted to evaluate the efficacy and safety of VLN (300 mg once weekly) as compared to placebo in adult patients with FCS.

Trial Design

Study CS6-pivotal was designed as an international, randomized, placebo-controlled trial in adults with FCS. Eligible patients entered a screening period of up to 8 weeks, which included a diet stabilization period of at least 6 weeks, followed by a 52-week treatment period during which patients were assigned to either VLN 300 mg (1.5 mL) subcutaneously once weekly or matching volume of placebo. Patients were equally allocated to VLN or placebo and stratified by history of pancreatitis and concurrent use of TG-lowering agents (fibrates and/or prescription omega-3 fatty acids). The primary efficacy parameter was percentage change in fasting TG from Baseline to Month 3 (average of Week 12 and Week 13 fasting assessments). At the end of the 52-week treatment period, patients either elected to enroll in an open-label extension study (CS7-OLE) or alternatively entered a 13-week post-treatment evaluation period. During the treatment period, patients reported to the study center for clinic visits a minimum of 5 times. Patients who discontinued early from the treatment period were encouraged to attend applicable landmark visits. Home health nurses could obtain blood

samples in between clinic visits. No lipid-lowering therapies could be started or adjusted after screening. Plasma apheresis was not allowed during the study.

Dose regimen adjustment or dose pauses were allowed for safety and tolerability but were not to occur unless necessary prior to the primary analysis time point (Month 3).

Landmark Dates

First patient screened	27 August 2014
First patient dosed	22 December 2014
Last patient enrolled	8 January 2016
Last patient last dose	19 December 2016
Data cut-off date	18 January 2017
Database lock (for primary analysis)	7 February 2017

Source: CSR CS6-pivotal, Response to IR 15 December 2017

Eligibility Criteria

Inclusion Criteria

Patients were eligible to participate in this study if they met the following inclusion criteria:

1. Age ≥ 18 years
2. History of chylomicronemia as evidenced by documentation of lactescent serum (a creamy top layer after ultracentrifugation of a fasting blood sample) or documentation of fasting TG ≥ 880 mg/dL
3. A diagnosis of FCS (Type 1 hyperlipoproteinemia) by documentation of at least one of the following:
    a. Confirmed homozygote, compound heterozygote, or double heterozygote for known loss-of-function mutations in Type 1-causing genes (such as *LPL*, *APO-CII*, *GPIHBP1*, or *LMF1*)
    b. Post-heparin plasma LPL activity ≤20% of normal
4. Fasting TG ≥ 750 mg/dL at Screening. If fasting TG was <750 mg/dL, up to 2 additional tests may have been performed in order to qualify
5. History of pancreatitis (defined as a documented diagnosis of acute pancreatitis or hospitalization for severe abdominal pain consistent with acute pancreatitis for which no alternate diagnosis was made). Patients without a documented history of pancreatitis were also eligible (enrollment capped at 28% - ≤20 of the 70 planned patients).
6. Adhere to a diet comprising ≤20 grams fat per day during the study

Exclusion criteria

Patients were to be excluded from enrolling in the study if they had any of the following exclusion criteria:

1. Diabetes mellitus with any of the following:

   a. Newly diagnosed within 12 weeks of Screening
   b. HbA1c ≥9% at Screening
   c. Recent change in or anticipated need to change anti-diabetic pharmacotherapy
   d. Use of glucagon-like peptide 1 agonists
2. Severe hypertriglyceridemia other than due to FCS
3. Active pancreatitis within 4 weeks prior to Screening
4. History within 6 months of Screening of acute or unstable cardiac ischemia or major surgery within 3 months of Screening
5. Any of the following laboratory values at Screening
   a. Hepatic: ALT or AST >2x ULN; total bilirubin>ULN
   b. Renal: Persistently positive for protein or blood on urine dipstick; estimated creatinine clearance <50 mL/min (Cockcroft and Gault formula)
   c. Cardiac Troponin I >ULN at Screening
   d. LDL-C>130 mg/dL at Screening
6. Uncontrolled hypertension (BP >160/100 mmHg)
7. History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters at Screening
8. Use of any of the following:
   a. Statins, omega-3 fatty acids (prescription or OTC), or fibrates unless on a stable dose for at least 3 months prior to Screening and dose and regimen to remain constant during the treatment period
   b. Nicotinic acid or derivatives of nicotinic acid within 4 weeks prior to Screening
   c. Systemic corticosteroids or anabolic steroids within 6 weeks prior to Screening unless approved by the Sponsor's Medical Monitor
   d. Glybera gene therapy within 2 years prior to Screening
   e. Oral anticoagulants (e.g. warfarin, dabigatran, rivaroxaban, and apixaban), unless on a stable dose for at least 4 weeks prior to Screening and regular clinical monitoring was performed
   f. Tamoxifen, estrogens or progestins, unless on a stable dose for at least 4 months prior to Screening and dose and regimen expected to remain constant during the treatment period
   g. Plasma apheresis within 4 weeks prior to Screening or planned during the study
9. Blood donation of 50 to 499 mL within 30 days of Screening or of >499 mL within 60 days of Screening
10. Known hypersensitivity to any of the excipients of the Study Drug

Reviewer Comment: Clinically, patients with FCS may be initially identified by clinical signs and symptoms. However, it is recommended that clinical suspicion of FCS be confirmed with genetic analysis describing either a known pathogenic variant or in case of a novel variant, supportive testing (i.e. LPL activity) to assess potential pathogenicity. In the CS6-pivotal trial, there were

examples of patients with a clinical phenotype suggestive of FCS and history of low LPL activity but whose on-study genetic and/or biochemical testing failed to confirm FCS, suggesting that an accurate diagnosis is a challenge even in a clinical trial where investigators would be expected to be especially expert in this condition. Given the risks associated with VLN, identifying the correct population of patients to be treated is important.

Strengths of these inclusion/exclusion criteria include permitting stable background lipid lowering medication, enrichment for patients with a history of pancreatitis, and the absence of restrictions on baseline platelet values, thereby permitting an evaluation of the effect of VLN in a patient population that should be representative of the target population.

Blinding

The applicant and all patients, monitors, and study center personnel were to be masked to treatment assignment and relevant laboratory values throughout the study until all patients had completed the treatment period and the Week 52 assessments (and post-treatment follow-up visits, where applicable) and the database had been locked.

Reviewer Comment: Although lipid panel results were not made available to patients or study personnel, it is possible based on the change in qualities of the blood with treatment (i.e. no longer grossly lipemic), and high incidence of injection site reactions, treatment assignment could have been unmasked. It is also possible that unblinding could have occurred due to knowledge of a patient's platelet count (refer to Review of Safety).

Review Committees

This trial included an independent Data and Safety Monitoring Board (DSMB), an adjudication committee for major adverse cardiovascular event (MACE), and a pancreatitis adjudication committee (PAC). Relevant details regarding adjudication are presented later in this review, as needed.

Study Endpoints

Primary Endpoint

The percentage change in fasting TG from Baseline to Month 3 (average of fasting assessments at the beginning of Weeks 12 and 13) was the primary efficacy parameter in CS6-pivotal.

Lowering TG among patients with severe hypertriglyceridemia is expected to reduce the risk for pancreatitis, and TG lowering has been the rationale for approving other drugs for severe hypertriglyceridemia (TG >500 mg/dL) over several decades, such as fibrates and prescription drugs derived from fish oil. Gallstones and alcohol use are the most common risk factors for pancreatitis, followed by hypertriglyceridemia, which may account for 1 to 4% of cases.[26] The absolute risk of pancreatitis based on serum TG thresholds has not been clearly defined;

[26] Scherer J et al. Issues in hypertriglyceridemic pancreatitis: an update. J Clin Gastroenterol. 2014;48(3):195

however, increased risk for pancreatitis is noted when TG levels are >1000 mg/dL.

Secondary Endpoints

Secondary endpoints evaluated in Study CS6-pivotal are included below. The applicant rank prioritized and used a sequential closed testing procedure:

1. Treatment response rate – responder defined as TG <750 mg/dL at the primary analysis point (3 months)
2. Percent change in fasting TG at 6 months (average of Week 25 and Week 26)
3. Percent change in fasting TG at 12 months (average of Week 50/51, and Week 52)
4. Average of maximum intensity of reported abdominal pain during the treatment period
5. Postprandial TG area under the curve change from Baseline to on-treatment measures (between Week 13 and Week 19)
6. Treatment response rate – responder defined as ≥40% TG reduction at the primary analysis point (3 months)
7. Absolute change in fasting TG at the primary analysis time point
8. Frequency of composite of episodes of acute pancreatitis and patient reported abdominal pain during the treatment period
9. Change in hepatic volume as assessed by MRI at Week 52

Exploratory endpoints included changes in other lipid/lipoprotein parameters, frequency of xanthoma, lipemia retinalis, change in post-heparin LPL mass and activity, and adjudicated acute pancreatitis event rate before and after treatment with VLN.

The following *efficacy* assessments were not pre-specified analyses and were added after the database lock for the primary analysis of 7 February 2017 and after the final SAP (dated 28 February 2017).

- Analysis of the reduction in the pancreatitis event rate in a subset of patients with a history of recurrent pancreatitis events (≥2 events in the 5 years before Study Day 1)
- Analysis of the change in average of maximum intensity of patient reported abdominal pain during on-treatment period in which missing data were imputed as 0.
- Analysis of episodes of moderate/severe abdominal pain, any abdominal pain, and worst pain during the first 3 months and after 3 months of on-treatment period for full analysis set and subset of patients reported any abdominal pain during Screening period and after 6 months of on-treatment period for completer set and subset of completed patients reported any abdominal pain during the Screening period.
- Additional analysis set defined as a completer set was defined as all patients who completed the study.
- Triglyceride data summarized by subgroup of patients who completed treatment and had dose adjustment or dose pause during the study, patients who completed treatment without dose adjustment or dose pause during the study, and those who withdrew early to explore the dosing effect on primary endpoint.

- Analysis on quality of life questionnaires, SF-36, and EQ-5D results in a subset of patients who reported any abdominal pain during the screening period, and subset of patients who had pre-dose adjudicated pancreatitis events.

Statistical Analysis Plan

Please see the statistical review team's assessment of the VLN application for details regarding the statistical analysis plan.

Protocol Amendments

The original protocol, dated 6 June 2014, was amended 8 times. The most relevant changes could affect the interpretation of safety data, since enhanced platelet monitoring plan was implemented via an Urgent Safety Measures letter dated 27 May 2016 and Protocol Amendment 6 (June 6, 2016) after reports of two SAEs of platelet count <25,000/mm^3; therefore, these changes will be discussed in the safety section of this review.

5.1.2. Study Results

Patient Disposition

A total of 130 patients were screened for CS6-pivotal and 63 (48%) failed screening; the reasons are enumerated in Table 4. Of the 46 who did not meet the inclusion/exclusion criteria, 19 did not have a diagnosis of FCS by documentation of genetic or LPL activity tests or a fasting TG ≥ 750 mg/dL at Screening.

A total of 67 patients were randomized to receive VLN (33 patients) or placebo (34 patients). All received study drug except one patient randomized to placebo.

A higher proportion (42%) of VLN-treated patients than placebo-treated patients (6%) permanently discontinued study drug prematurely. Adverse event was the most frequently cited reason for study drug discontinuation in the VLN group; no placebo-treated patients discontinued due to an adverse event.

Table 4. Patient Disposition – CS6-pivotal

Disposition	PBO n (%)	VLN 300 mg n (%)	All Patients n (%)
Patients Screened			130
Screen Failures			63 (48)[1]
Reason for Screen Failure			
Inclusion/Exclusion criteria			46 (73)[2]
Sponsor decision			9 (14)
Withdrawal of consent			6 (10)
Investigator decision			1 (2)
Other			1 (2)

Disposition	PBO n (%)	VLN 300 mg n (%)	All Patients n (%)
Patients Randomized	34	33	
Patients Dosed	33	33	
Patients Who Completed the Study Treatment	**32 (97)[3]**	**19 (58)[3]**	
Completed without drug interruption or reduced dose frequency	26 (79)	6 (18)	
Patients Who Discontinued Study Treatment	**1 (3)**	**14 (42)**	
Reason for Discontinuation			
Adverse event	0	9 (27)	
Voluntary withdrawal	1 (3)	4 (12)	
Investigator Judgment	0	1 (3)	
CS6 Patients who enrolled into CS7-OLE study (as of 18 Jan 2017)	**19 (58)**	**10 (30)**	
CS6 Patients who enrolled into CS7-OLE study (as of 31 Aug 2017)	**30 (91)**	**14 (42)**	
CS6 Patients remaining on treatment in CS7-OLE (as of 31 Aug 2017)	**24 (73)**	**9 (27)**	

Source: CSR CS6-pivotal Table 9
1 Percentage calculated with the number of patients screened as the denominator
2 Percentage calculated with the number of patients who failed screening as the denominator
3 Percentage calculated with the number of patients dosed as the denominator

Reviewer Comment: No placebo-treated patients discontinued due to an adverse event or required a dose adjustment (i.e., reduce to biweekly dosing). In contrast, a substantial number of patients treated with VLN discontinued study treatment (42%), with the highest proportion due to an adverse event. In addition, of the 19 VLN-treated patients who completed the study on treatment, only 6 remained on weekly 300 mg VLN dosing throughout the 52-week treatment period. The amount of data to support the proposed indicated treatment regimen of 300 mg weekly is therefore limited.

Protocol Violations/Deviations

Overall, 37 (55%) patients experienced a major protocol deviation including 15 (44%) patients in the VLN group and 22 (67%) patients in the placebo group. The most common major protocol deviations were related to patients being dosed despite having no valid platelet count within 14 days, as instituted in a Notice of Implementation of Urgent Safety Measures on 27 May 2016. This occurred in 18 placebo-treated and 4 VLN-treated patients.

Table of Demographic Characteristics

The table below lists the demographic characteristics of the 66 treated patients reported to have a clinical phenotype of FCS.

Table 5. Demographic/Baseline characteristics - CS6-pivotal

Demographic Parameters	Placebo N=33 n (%)	VLN 300 mg N=33 n (%)
Sex		
Male	14 (42)	16 (49)
Female	19 (58)	17 (52)
Age		
Mean years (SD)	46 (14)	47 (13)
Age Group		
< 17 years	0	0
≥ 17 - < 65 years	31 (94)	30 (91)
≥ 65 years	2 (6)	3 (9)
Race		
White	29 (88)	24 (73)
Black or African American	0	0
Asian	4 (12)	7 (21)
Other	0	2 (6)
Ethnicity		
Not Hispanic or Latino	26 (79)	26 (79)
Region		
United States	6 (18)	5 (15)
Rest of the World	27 (81)	28 (85)
Canada	8 (24)	6 (18)
Europe	18 (55)	18 (55)
Other	1 (3)	4 (12)
BMI (kg/m2)		
Mean	24.1	25.9

Source: Adapted from CS6-pivotal CSR Table 14.1.1.1

Reviewer Comment: Demographic characteristics were well-matched across the treatment groups. Although FCS has been described in all races,[27] most patients were non-Hispanic white adults. Approximately 17% of the population was studied in the U.S. Per the applicant, the presentation of FCS is consistent across regions and the standard of care is the same for the U.S. population and non-U.S. population.

[27] Burnett JR, Hooper AJ, and RA Hegele. "Familial Lipoprotein Lipase Deficiency." GeneReviews. https://www.ncbi.nlm.nih.gov/books/NBK1308/

Other Baseline Characteristics

Patients enrolled in CS6-pivotal qualified based on prior documentation of an FCS-associated genotype or based on prior documentation of LPL deficiency in association with other qualifying inclusion and exclusion criteria. Testing via next-generation sequencing of hypertriglyceridemia-related genes in the reference laboratory was offered to consenting patients, but was not a requirement of enrollment.

The applicant was asked to provide a breakdown of the 66 treated patients by presence or absence of genetic or LPL activity testing consistent with FCS that was done as part of the study.

Table 6. Results of On-Study Confirmatory Genetic or LPL activity Testing

Number of Patients		On-study Genetic Confirmation of FCS			
		Confirmed	Not Confirmed	Not Done	
On-study LPL Activity ≤20% of Normal	Yes	30	3	3	36
	No	16	5	0	21
	Missing	5	4	0	9
		51	12	3	Total: 66 Patients

Source: FDA Clinical Reviewer Table CS6 adsl.xpt; IR response 6 February 2018

Reviewer Comment: *Of the 66 patients enrolled in CS6-pivotal, 63 patients had genetic testing conducted as part of the study and 57 patients had LPL activity assessed by a research laboratory. Of the 63 patients who had genetic testing performed, 51 had mutations consistent with FCS (40 of whom had mutations in LPL). LPL activity was assessed in 46 patients who reportedly had genetic confirmation of FCS; interestingly, 16 (35%) of these patients did <u>not</u> have low LPL activity despite genetic support for an FCS diagnosis. LPL activity was also assessed in 8 of the 12 patients who did <u>not</u> have genetic confirmation of FCS; 5 (63%) of these 8 patients also did not have low LPL activity (i.e. LPL activity was >20% normal in these patients).*

Nine (14%) of the 66 patients enrolled in CS6-pivotal had neither confirmatory genetic testing nor abnormal LPL activity (Table 7). Per the applicant, these 9 patients had a "clinical phenotype" or FCS since all patients had at least 1 screening fasting TG >=750 mg/dL and 5 had a history of pancreatitis. For 3 of these 9 patients, the investigator believed that the patient had genetics consistent with FCS, but the study geneticist disagreed. The remainder either had inaccurate LPL activity testing or had on-study testing that did not corroborate the previously documented low LPL activity.

The indication proposed by the applicant does not include requirements for genetic testing or for documentation of low LPL activity (note: LPL activity is considered a research laboratory test). A fasting TG level ≥750 mg/dL alone is insufficient to describe a patient as having a "clinical phenotype of FCS."

Table 7. Patients Without Confirmatory Genetic or Functional Biomarker consistent with FCS – CS6-pivotal

Subject ID	(b) (6)								
Age Race/Sex	37 yo White/M	46 yo Asian/M	61 yo Asian/M	51 yo White/F	44 yo White/M	61 yo White/M	50 yo White/M	75 yo White/M	58 yo White/M
Baseline TG >880 mg/dL (Average)	N 631 mg/dL	N 780 mg/dL	Y 1171 mg/dL	Y 1328 mg/dL	Y 3846 mg/dL	Y 1527 mg/dL	Y 1039 mg/dL	Y 1115 mg/dL	Y 5391 mg/dL
Lipid lowering meds	Fenofibrate, rosuvastatin	N	Fenofibrate	Gemfibrozil	Fenofibrate	Ciprofibrate, pravastatin	Fenofibrate	N	Fenofibrate, omega 3-EE, atorvastatin
Diagnosis of FCS before 40 by medical history	N	N	N	N	Y	N	N	N	N
History of pancreatitis	N	N	Y (none in 5 years prior to study)	Y (1 adjudicated event in 5 years prior to study)	Y (none in 5 years prior to study)	Y (Two episodes in 5 years prior to study – adjudicated as "other" not confirmed events	N	N	Y (no adjudicated pancreatitis events in 5 years prior to study)
Other relevant med history	N	N	T2DM, CHD, CABG, HTN	Obesity, T2DM, HTN	T2DM, HTN	MI, HTN	N	HTN, hypothyroidism, T2DM	Diagnosed with hyperlipidemia at 2yo
TG/TC ratio>5	N	N	Y	N	Y	Y	N	Y	Y
ApoB <100 mg/dL	N 122 mg/dL	Y 86 mg/dL	Y 73 mg/dL	Y 96 mg/dL	Y 76 mg/dL	Y 66 mg/dL	N 110 mg/dL	Y 96 mg/dL	Y 74 mg/dL
Genetic confirmation **Central Reader Genetic Assessment**	N LPL heterozygous missense	N APOA5 simple homozygous common	N LPL simple heterozygous missense	N APOA5 2 heterozygous missense mutations in cis; 1 normal	N No mutations	N No mutations	N No mutations	N No mutations	N Simple heterozygote for a mutant LPL allele containing 2

Subject ID	[redacted] (b) (6)								
	mutation	polymorphism	mutation	allele					variants close together
Low post-heparin LPL activity	N	Not done	Not done	N	N	N	N	N	N
Study Eligibility	Based on low LPL activity as per the original study lab's assessment LPL activity subsequently not confirmed by reference lab Patient was excluded from PPS	Based on PI assessment of genetics Genetic diagnosis not confirmed by study expert	Based on medical history of no LPL activity	Based on low LPL activity as per the original study lab's assessment LPL activity subsequently not confirmed by reference lab	Based on local assessment of genetics and medical history of low LPL activity Genetic diagnosis not confirmed by study expert. Low LPL activity not confirmed by reference lab	Based on low LPL activity Pre-heparin sample used by error and low LPL activity was not confirmed in post-heparin samples Patient excluded from PPS	Based on low LPL activity Pre-heparin sample used by error and low LPL activity was not confirmed in post-heparin samples Patient excluded from PPS	Based on low LPL activity as per the original study lab's assessment LPL activity subsequently not confirmed by reference lab Patient excluded from PPS	Based on initial assessment of genetics Considered non-confirmatory by study expert geneticist

Source: CS6-Addendum 1 Table 2; CS6 adsl.xpt

Medical Disease History

Patients participating in CS6-pivotal were queried for other features of FCS and prior lipid-lowering strategies in their medical history.

Table 8. Medical Disease History/Prior Lipid-Lowering Therapies – CS6-pivotal Safety Set

Demographic Parameters	Placebo N=33 n (%)	VLN 300 mg N=33 n (%)
Documented Diagnosis of Pancreatitis	26 (79)	24 (73)
Lipemia retinalis	9 (27)	5 (15)
Eruptive xanthomas prior to screening	9 (27)	6 (18)
History of type 2 DM	4 (12)	6 (18)
Treated with Glybera	5 (15)	2 (6)
Treated with Fibrates	15 (46)	17 (52)
Treated with Statins	4 (12)	9 (27)
Treated with Omega-3-Fatty Acids	9 (27)	10 (30)

Source: CSR CS6-pivotal Table 14, 16

Reviewer Comment: As shown in the table above, 50 (76%) of patients had a history of pancreatitis, consistent with prevalence estimates in published literature.
Most patients did not have a history of lipemia retinalis or xanthomas, which is also reflected in the low proportion of patients exhibiting these features at baseline; only 1 placebo-treated patient had a xanthoma recorded at baseline.
Seven patients were treated with Glybera (alipogene tiparvovec), which is an adeno-associated virus-based gene therapy vector designed to deliver a normal human LPL gene to muscle cells, to correct the LPL enzyme deficiency. In October 2012, the European Medicines Agency authorized marketing of Glybera under "exceptional circumstances" for treatment of patients with genetically confirmed LPLD, detectable levels of LPL protein, and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. In 2017, Glybera was removed from the European market citing limited usage.[28]
The average time interval from Glybera administration to enrollment in CS6-pivotal was 8 years among these 7 patients. At baseline, the median TG in this group was 1583 mg/dL. Due to the small number of Glybera-treated patients in this study (only two patients with a history of Glybera treatment received VLN treatment) and the uncertainty regarding Glybera's efficacy, the impact Glybera treatment may have had, if any, on VLN's treatment effect could not be reliably discerned.
The type of prior lipid-lowering medications used in this population was expected given that these medications are approved for treatment of hypertriglyceridemia, even though it is generally recognized that these classes of medications are typically ineffective in lowering TG among patients with FCS.

[28] https://tools.eurolandir.com/tools/Pressreleases/GetPressRelease/?ID=3330232&lang=en-GB&companycode=nl-qure&v= uniQure Press Release. uniQure Announces It Will Not Seek Marketing Authorization Renewal for Glybera in Europe. 20 April 2017; Accessed 13 November 2017

Baseline Lipid Parameters

As shown in the table below, following the diet stabilization period, patients had elevated fasting mean and median TG values. The baseline metabolic lipid profile of extremely high serum triglycerides and chylomicrons (as assessed by apoB-48) and relatively low HDL-C and LDL-C is characteristic of patients with FCS.

Table 9. Baseline Lipid Parameters – CS6-pivotal

Lipid parameters[1]	Placebo N=33	VLN 300 mg N=33
TG (mg/dL)		
Mean (SD)	2152 (1153)	2267 (1259)
Median (P25, P75)	2012 (1130, 3026)	1891 (1328, 3098)
Apo B-48 (mg/dL) [NR: 0.15-0.83 mg/dL]	9.3	11.2
Apo C-III (mg/dL) [NR: 5-20 mg/dL]	29	31
Non-HDL-C (mg/dL)	267	276
HDL-C (mg/dL)	17	17
VLDL-C (mg/dL) [NR: 0-29 mg/dL]	41	40
LDL-C (mg/dL)	28	28
apoB (mg/dL)	69	65

NR: Normal Range
1 Mean values presented unless otherwise noted. The baseline for fasting lipid measurements is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 pre-dose assessment. If one of the two measurements is missing, then the other measurement is assigned as the baseline value.
Source: CSR CS6-pivotal Table 18

Baseline Patient-Reported Assessments

Although recurrent pancreatitis can occur among patients with FCS, patients also describe recurrent abdominal symptoms that may be self-treated by further dietary restriction or skipping meals, without seeking medical attention.

A summary of patient-reported abdominal pain during the screening period, which lasted at least 6 weeks, is presented in

Table 10. Abdominal pain intensity was to be reported weekly by patients using a questionnaire developed by the applicant. Pain was rated on a scale of 0 to 10 (10 representing the worst pain). If a patient did not experience any pain, the score was entered as 0.

Table 10. Patient-Reported Abdominal Pain During Screening – CS6-pivotal

Abdominal Pain During Screening Period	Placebo N=33 n (%)	VLN 300 mg N=33 n (%)
Number of patients with any reported Abdominal Pain	10 (30)	7 (21)
Average of Weekly Maximum Intensity of Abdominal Pain	0.79	0.54
Worst Weekly Maximum Intensity of Abdominal Pain		
0	22 (67)	24 (73)
1-3 (mild)	2 (6)	2 (6)
4-6 (moderate)	4 (12)	3 (9)
7-10 (severe)	4 (12)	2 (6)
Missing	1 (3)	2 (6)

Source: CSR CS6-pivotal Table 15

Reviewer Comment: In previous descriptions of the experience of living with FCS, patients have listed recurrent abdominal pain as a significant factor limiting their activities. Therefore, it is surprising to this reviewer that most patients did not report any abdominal pain during the 6- to 8-week screening period using this PRO. Furthermore, of the patients reporting pain at least once during this period, the worst weekly maximum intensity was generally characterized as mild to moderate. Only six (9%) patients, overall, reported their worst weekly maximum pain intensity as ≥7 on the 10-point scale. Although it is unclear if the scale used to characterize pain was valid because, according to the FDA Clinical Outcomes Assessment (COA) reviewer, the applicant did not obtain patient input to determine if the instrument included the most important symptoms or associated symptom impacts for the population before using it in the trial.

The applicant did not attempt to systematically assess any other disease-specific symptoms among FCS patients (e.g., physical symptoms such as fatigue, cognitive symptoms such as memory impairment, or emotional symptoms such as anxiety or depression).

Efficacy Results – Primary Endpoint

See Dr. Cambon's statistical review for a thorough discussion of the efficacy of VLN. Selected analyses from the applicant will be presented in this clinical review; Dr. Cambon discusses relevant limitations separately.

Table 11 presents the results for mean percent change from baseline to the Month 3 endpoint in fasting TG; there were no missing TG values in this analysis, although 2 patients assigned to VLN had discontinued study drug before Week 13. At 3 months, patients assigned to VLN had a mean reduction in TG of 77% from Baseline compared to a mean increase of 18% in placebo-treated patients (P<0.0001).

Table 11. Mean Percent Change from Baseline to Month 3 in Fasting TG (mg/dL)-Applicant Analysis

Month 3	Statistic	Placebo N=33	VLN 300 mg N=33
Baseline (mg/dL)	Mean (SD)	2152 (1153)	2267 (1259)
Month 3 (mg/dL)	Mean (SD)	2367 (1315)	590 (497)
% Change from BL	LS Mean (95% CI)	17.6 (-4, 39.2)	-76.5 (-97.4, -55.5)
Treatment Comparison from ANCOVA model			
Absolute Difference in % Change		-94.1	
95% CI		(-121.7, -66.6)	
p-value		<0.0001	

Source: CSR CS6-pivotal; Table 20
Note: p-value of Shapiro-Wilk normality test based on observed data was <0.0001.

A sensitivity analysis using the Wilcoxon-rank sum testing and the Hodges-Lehmann estimator demonstrated similar findings to the primary statistical analysis with a median percent change from Baseline with VLN treatment at 3 months of 78%.

There were no meaningful differences in mean percent change from Baseline in TG at Month 3 when evaluated by presence or absence of concurrent use of fibrates and/or omega-3 fatty acids. VLN-treated patients on fibrates and/or omega-3 fatty acids demonstrated a 76% mean percent change reduction in TG from Baseline; without these background drugs, VLN-treated patients demonstrated a 73% mean percent change reduction in TG from Baseline.[29]

Efficacy Results – Other Endpoints/Analyses of Interest

Distribution of Fasting TG at Month 3

The empirical cumulative distribution function for fasting TG values observed at Month 3 is shown in **Error! Reference source not found.**.

[29] CSR CS6-pivotal Table 14.2.1.2.1.c

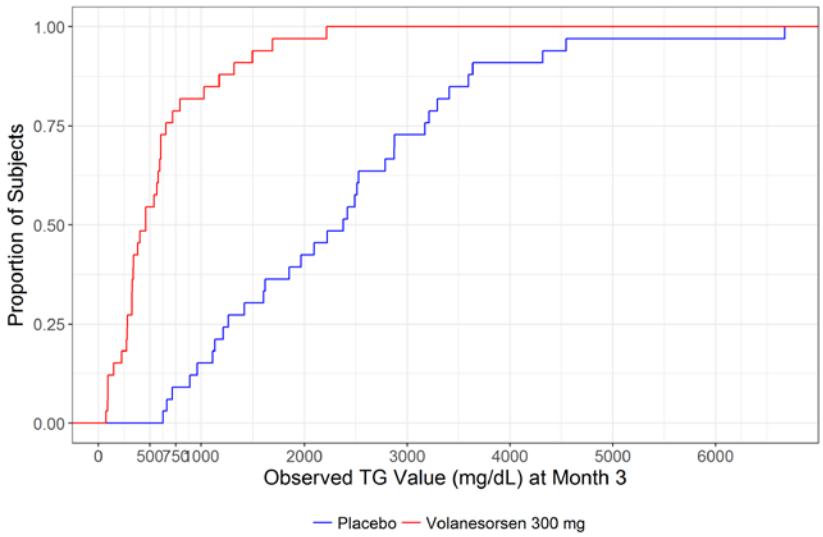


Figure 3. Empirical Cumulative Distribution for Observed Fasting TG at Month 3– CS6-pivotal
Source: Created from CS6 *adeff1.xpt*

Distribution of Percent Change in Fasting TG at Month 3

The empirical cumulative distribution function for percent change in TG from baseline to Month 3 is shown in Figure 4.

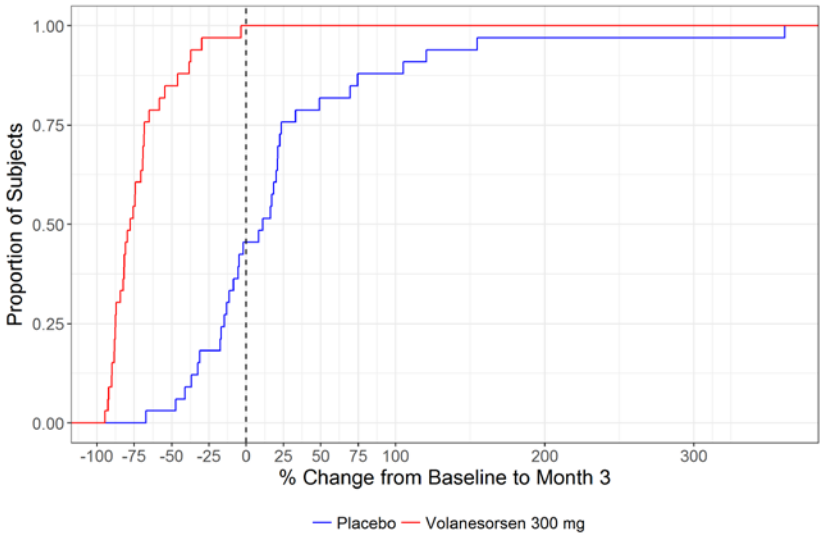


Figure 4. Empirical Cumulative Distribution for % Change in TG at Month 3 - CS6-pivotal
Source: Created from CS6 *adeff1.xpt*

Percent change in fasting TG at Month 6 and Month 12

Significant reductions in fasting TG were observed in VLN-treated patients at Month 6 and 12 timepoints. In the applicant's analyses, the mean percent change from baseline was 53% and

40% in VLN-treated patients at Month 6 and Month 12, respectively. The percent decreases from baseline at these timepoints were numerically smaller than the changes observed at Month 3, which may be attributable to increasing proportion over time of patients with dose adjustments and treatment discontinuation who provided TG measurements.

The applicant's analysis used a multiple imputation approach assuming those with missing data at months 6 and 12 would behave the same as those who continued in the study. This assumption tends to overestimate the treatment effect in this population, as one would expect those who discontinue volanesorsen treatment to have higher TG levels than those who continue treatment. In the table below, the FDA statistical reviewer estimated that treatment with VLN reduced TG 33% from baseline to Month 12 compared to a 12% increase for placebo, using a multiple imputation model for missing data; this treatment difference was statistically significant. See Dr. Cambon's review for the FDA-preferred analysis using washout imputation instead of an imputation technique that assumes missing data are missing-at-random.

Table 12. Primary and Secondary Endpoint Results: Percent Change in TG at 3, 6 and 12 Months (FDA Analysis)

Month	Placebo (N=33)		Volanesorsen (N=33)		Mean Difference (95% CI)	Mean Difference (95% CI)
	n	Adjusted Means	n	Adjusted Means	Washout Imputation* Used for 6 and 12 months	Imputation based on MAR assumption**
3	33	17.6	33	-76.5	-94.1 (-121.7, -66.6)	-94.1 (-121.7, -66.6)
6*	31	24.4 *	29	-47.5*	-71.9* (-95.3, -48.6)	-77.8** (-106.4, -49.1)
12*	32	11.9*	27	-32.7*	-44.6* (-70.4, -18.7)	-49.1** (-94.7, -3.5)

*Multiple imputation – missing final assessment values on VLN and placebo arms imputed based on placebo ANCOVA model. ** Source- Applicant Study Report; Multiple imputation – missing final assessment values on VLN and placebo arms based on ANCOVA model. Abbreviations: MAR- Missing at Random.
Source: FDA Statistical Review

The applicant and FDA conducted responder analyses at Month 3, Month 6, and Month 12. As seen with previous analyses the numbers favor the VLN treated group compared to the placebo group, but the proportion of patients or magnitude of effect attenuates, likely due to discontinuation and dose adjustment. Further details may be found in the FDA Statistical Review.

Table 13. Responder Analysis With Non-Responder* Imputation (FDA analysis)

TG Threshold	Time	Placebo (N=33) n (%)	Volanesorsen (N=33) n (%)	Unadjusted OR (Exact 95% CI)*
≥20% TG Reduction	Month 3	6 (18.2%)	32 (97%)	144.0 (15.8, 6067.4)
	Month 6	5 (15.2%)	26 (78.8%)	20.8 (5.1, 91.1)
	Month 12	10 (30.3%)	22 (66.7%)	4.6 (1.5, 14.8)
≥30% TG Reduction	Month 3	6 (18.2%)	31 (93.9%)	69.8 (11.4, 679.2)
	Month 6	2 (6.1%)	26 (78.8%)	57.6 (9.8, 555.3)
	Month 12	6 (18.2%)	22 (66.7%)	9.0 (2.5, 33.8)

TG Threshold	Time	Placebo (N=33) n (%)	Volanesorsen (N=33) n (%)	Unadjusted OR (Exact 95% CI)*
≥40% TG Reduction	Month 3	3 (9.1%)	29 (87.9%)	72.5 (12.6, 491.0)
	Month 6	1 (3%)	24 (72.7%)	85.3 (10.2, 3613.2)
	Month 12	3 (9.1%)	21 (63.6%)	17.5 (3.9, 103.0)

*Dropouts imputed as non-responders
Source: FDA Statistical Review

Subgroup analysis of Change in TG

Pre-specified subgroup analyses of gender, race, age, ethnicity, and region on response to VLN were conducted. Given the small study population, the number of patients in the different categories comprising the race, age, and ethnicity subgroups were very small. For example, only 5 patients in CS6-pivotal were 65 years or older. Overall, there were no substantial differences identified in mean percent change from Baseline to Month, 3, Month 6, and Month 12 endpoints across these subgroups.

Abdominal Pain

The collection of weekly maximum intensity of abdominal pain was previously described. The average of these weekly values during the treatment period was compared between the two treatment groups using a two-sample t-test. Missing values were pre-specified to be imputed using Next Observation Carried Back (NOCB); i.e., if a patient did not complete the questionnaire for several weeks, the next value entered was assumed to have occurred during all intervening (missing) weeks.

In the pre-specified secondary endpoint analysis of overall change in the frequency and severity of patient-reported abdominal pain, there were no differences detected between placebo and VLN-treated patients. See Dr. Cambon's review for additional discussion.

Table 14. Summary of Patient-reported Abdominal Pain with NOCB imputation (pre-specified) – CS6-pivotal

	Placebo N=33	VLN 300 mg N=33
Patients with Any Reported Abdominal Pain Event On-treatment	**14 (42%)**	**15 (46%)**
Average of Maximum Intensity of Reported Abdominal Pain During the On-treatment Period		
N	33	33
Mean	0.36	0.38
p-value	0.9	
Worst Maximum Intensity of Reported Abdominal Pain During On-Treatment Period		
N	33	33
Mean	2.7	2.3
Worst Maximum Intensity of Weekly Reported Abdominal Pain During On-Treatment Period		
0	19 (58%)	18 (55%)

	Placebo N=33	VLN 300 mg N=33
1-3 (mild)	1 (3%)	4 (12%)
4-6 (moderate)	5 (15%)	6 (18%)
7-10 (severe)	8 (24%)	5 (15%)

Source: CSR CS6-pivotal; Table 28

Reviewer Comment: These results do not provide evidence for benefit from VLN treatment on the patient-reported outcome of abdominal pain. The small numerical differences in the proportion of patients reporting their "worst maximum intensity of weekly reported abdominal pain" as "severe" is not strong evidence of a VLN-treatment effect, in this reviewer's opinion.

The applicant conducted similar exploratory analyses using the subgroup of 17 patients who had reported any abdominal pain during the screening period. Furthermore, these subgroup analyses were repeated with an unplanned imputation method (imputing "0" for any missing values). The results of these analyses are shown in the tables below.

Table 15. Change from Baseline in Average of Weekly Maximum Intensity of Patient-reported Abdominal Pain in Subgroup of Patients with Abdominal Pain During Screening Period

		Pre-specified NOCB Imputation		Not pre-specified Missing Data as 0 Imputation	
	Statistic	Placebo	VLN	Placebo	VLN
Baseline					
	N	10	7	10	7
	Mean (SD)	2.53 (1.67)	2.39 (2.19)	1.45 (1.30)	2.25 (2.23)
On-treatment					
	Mean (SD)	1.02 (1.21)	0.65 (0.86)	0.95 (1.09)	0.62 (0.80)
Change from Baseline	LS Mean (95% CI)	-1.97 (-2.59,-1.34)	-2.53 (-3.37, -1.70)	-1.33 (-2.10, -0.56)	-2.28 (-3.33, -1.23)
Treatment Comparison					
Difference		-0.57		-0.95	
95% CI		(-1.21, 0.07)		(-1.75, -0.16)	
p-value		0.0774		0.0227	

Source: CSR CS6-pivotal; Table 29, Table 30

Reviewer Comment: In the subset of patients who reported any abdominal pain during the Screening period, the applicant reports a "statistically significant" reduction in the average of weekly maximum intensity of abdominal pain among VLN-treated patients compared with placebo-treated patients, when missing questionnaires are imputed as "0" (no pain) (p=0.02). This analysis may be nominally statistically significant; however, it is this reviewer's opinion that this result is not convincing given that the analysis was not pre-specified, the sample size of the subgroup is small because most patients reported no abdominal pain during screening, the observed changes are extremely small and unlikely to be clinically meaningful, and the nominal statistical significance is sensitive to the imputation technique for missing data (with a post hoc method being the one that achieves "statistical significance"). Furthermore, the missing data assumptions in this analysis are problematic. The analysis relies on a missing-at-random assumption for missing data after patient dropout (a questionable assumption given the greater

dropout on VLN than placebo), as well as the likely implausible assumption that missing weekly scores in patients remaining in the study were all zeroes (i.e., none of these patients had any pain during those missing weeks).

The applicant performed additional exploratory subgroup post-hoc analyses looking at the frequency of moderate/severe abdominal pain, any abdominal pain, and worst maximum intensity of abdominal pain in different time periods (months 0-3, months 4-12, and months 7-12) in patients that reported abdominal pain during the screening period (at most, 17 patients). The applicant contends there is a "trend" towards a reduction in frequency of abdominal pain during months 7-12 of treatment (3 vs. 11 events per patient per year in VLN and placebo groups, respectively); in the frequency of episodes of moderate to severe abdominal pain during months 4-12 (2 vs. 5 events per patient per year) and during months 7-12 (2 vs. 7 events per patient per year); and in worst abdominal pain intensity during months 4-12 (mean 3.14 vs. 5.4) and during months 7-12 (mean 2.4 vs. 5.4).

Reviewer Comment: This was a small, post hoc subgroup analysis that should be interpreted with substantial caution. Only 7 VLN-treated patients contributed to analyses for periods beginning at month 4, and only 5 VLN-treated patients contributed to analyses for the 7-12 month period. In addition, the 4-12 month and 7-12 month time periods overlap, so the suggestion that there is a trend in reduction over time is not supported by these data. Furthermore, note that any analyses of binary outcomes (e.g., the proportion of patients with some degree of pain) are likely biased in favor of VLN because these are "on-treatment" analyses; given the greater exposure in the placebo group resulting from fewer premature discontinuations, patients assigned to placebo have more time at risk for events, particularly in later time periods of the study.

Composite of Acute Pancreatitis and Patient-Reported Abdominal Pain

There were no treatment differences observed for the composite of adjudicated acute pancreatitis and/or patient-reported moderate/severe abdominal pain. Twelve patients in the VLN group and 13 patients in the placebo group had at least one of these events. The incidence rate (events per patient-year) was not different between VLN-treated and placebo-treated patients (p=0.6).

Table 16. Composite of Acute Pancreatitis and/or Patient-Reported Moderate/Severe Abdominal Pain During On-treatment period – CS6-pivotal

	Placebo N=33	VLN 300 mg N=33
Patients with Acute Pancreatitis and/or Moderate/Severe Abdominal Pain	13 (39%)	12 (36%)
Events per Patient-Year	2.0	2.7
p-value	0.6	

Source: CSR CS6-pivotal, Table 34

Adjudicated Acute Pancreatitis

A dedicated committee, blind to treatment assignment, adjudicated relevant SAEs according to the Atlanta classification of acute pancreatitis. In addition, retrospective chart review was conducted in an attempt to capture any events of acute pancreatitis during the 5 years preceding first dose; these events were also adjudicated. Each event was assigned to one of the following groups: Documented pancreatitis, Probable pancreatitis, Possible pancreatitis, and "Other." Two members would independently review a case; if there was disagreement, the case was adjudicated by consensus during a meeting involving 4 members.

In CS6-pivotal, from the first dose of study drug through the end of the study, 1 (3%) VLN-treated patient experienced 1 event of adjudicated acute pancreatitis and 3 (9%) placebo-treated patients experienced 4 events (p = 0.6). All events occurred during the "on-treatment" period (last dose + 28 days); the event in the VLN-treated patient occurred 9 days after discontinuation of dosing.

The applicant performed a post hoc subgroup analysis of adjudicated pancreatitis events pre- and post-treatment in patients with a history of recurrent pancreatitis events. When the applicant only considered those with a history of at least *two* adjudicated events of pancreatitis in the 5 years prior to treatment, they claimed a statistically significant effect of VLN on treatment-emergent acute pancreatitis (nominal P=0.02).

Table 17. Treatment-emergent Acute Pancreatitis Overall and in Subset of Patients with ≥2 Pre-dose Events of Acute Pancreatitis (All Events Adjudicated)

	Placebo N=33		VLN 300 mg N=33		Nominal P-value
	n/N	# Events	n/N	# Events	(Comparing # Patients)
Treatment-emergent pancreatitis (pre-specified analysis)	3/33	4 events	1/33	1 event	0.6
Treatment-emergent pancreatitis among those with history of ≥2 pre-treatment pancreatitis events (post-hoc analysis)	3 / 4	4 events	0 / 7	0 events	0.02

Source: CSR CS6-pivotal; Table 54
Prior-treatment event: Any adjudicated event starting before the first dose of study drug
Treatment-emergent event: Any adjudicated event starting on or after the first dose of study drug
Odds ratio, 95% CI, and p-value calculated with Fisher's exact test

Reviewer Comment: In addition to concerns regarding the exploratory, unplanned nature of the analysis limited to patients with a history of ≥2 pre-treatment events (including concerns regarding multiplicity), it is unknown whether all patients with a history of recurrent pancreatitis (and the events themselves) were identified given the retrospective nature of the data collection. Furthermore, this is an analysis comparing proportions, which is problematic and biased in favor of VLN due to greater dropout and therefore lesser at-risk time for VLN.

Hepatic and Splenic Volume

Hepatic volumes in patients with normal healthy livers average 1106 cm^3 (range 553 to 2417 cm^3).[30] At baseline, both hepatic and splenic volumes as assessed by MRI were increased. Hepatosplenomegaly is a characteristic found in patients with FCS. Hepatic and splenic volumes increased from baseline to Week 52 in the VLN-treated group compared with placebo, with the change in splenic volume being particularly notable (p=0.0001).

Reviewer Comment: It is unclear what significance these changes in hepatic or splenic volume may have in this patient population. The applicant noted that there was a small inverse correlation between change from baseline in spleen size and maximum change from baseline in platelet count when data from CS6-pivotal and CS16-HTG were combined. It is unknown to what extent the increase in splenic size associated with VLN treatment contributes to the platelet reduction, but it is plausible that splenic sequestration plays some role.

Table 18. Change from Baseline in Hepatic and Splenic Volume at Week 52 with Multiple Imputation – CS6-pivotal

	Baseline Mean		Change from Baseline LS Mean		Relative Difference	p-value
	Placebo	VLN 300 mg	Placebo	VLN 300 mg		
Hepatic Volume (cm^3)	1959	2063	-25	113	138	0.1
Hepatic Fat (%)	5.7	8.6	0.1	-1.7	-1.8	0.09
Splenic Volume (cm^3)	454	508	32	107	75	0.0001

Source: CS6-pivotal; Table 35, 36

Frequency of Eruptive Xanthoma and Lipemia Retinalis

None of the VLN-treated patients had eruptive xanthomas at Baseline or during the treatment period; 1 placebo-treated patient had eruptive xanthoma at Baseline and 1 placebo-treated patient had eruptive xanthoma (mild) during the treatment period.

Sixteen (24%) of the 66 patients treated in CS6-pivotal had lipemia retinalis noted at Screening: 10 VLN, 6 placebo. Among this subgroup, 9 (90%) of the 10 VLN-treated patients showed improvement at Week 52 compared with 4 (67%) of the 6 placebo-treated patients. Among the 55 total patients assessed at Week 52, only 1 (3.4%) of 29 placebo-treated patients had lipemia retinalis compared with 1 (3.8%) of 26 VLN-treated patients.

Reviewer Comment: Too few events were noted to make a robust conclusion regarding the treatment effect of VLN on lipemia retinalis. Lipemia retinalis is typically not associated with visual impairment and appears to have no clinical sequelae; no routine testing of visual parameters was conducted.[31]

[30] Verma SK et al. Simple linear measurements of the normal liver: interobserver agreement and correlation with hepatic volume on MRI. Clinical Radiology;2010 (65):315-18

[31] Brunzell JD & Bierman EL. Chylomicronemia syndrome. Interaction of genetic and acquired hypertriglyceridemia. The Medical clinics of North America;1982(66)2:455-68

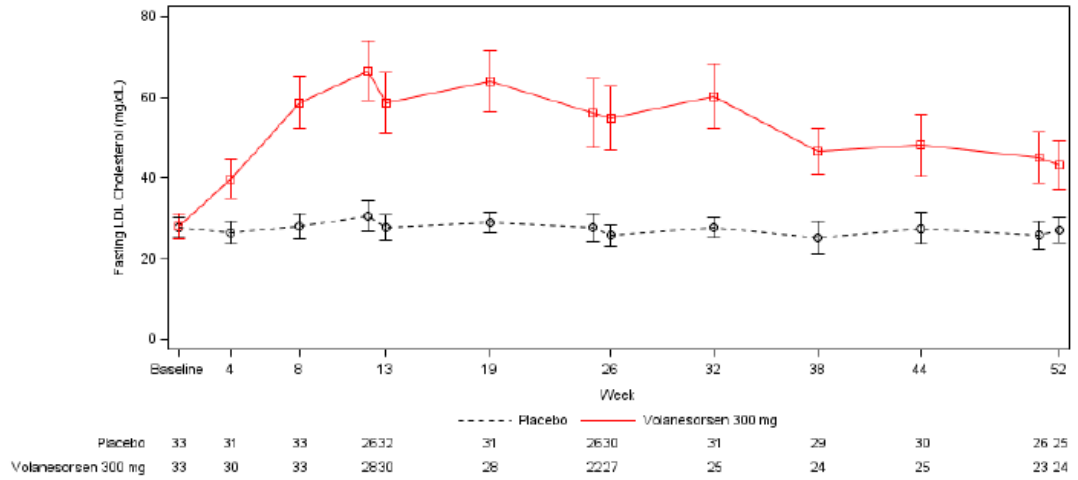
Lipid parameters

Mean % changes from baseline in lipid parameters other than TG are shown in the table below. The observed increases in LDL-C are consistent with the effects of other TG-lowering medications in patients with severe hypertriglyceridemia. The mean LDL-C values remained below 70 mg/dL (Figure 5), although some patients had marked increases. Non-HDL-C falls, on average, although apo B increases. The net effect on atherosclerotic risk is unknown. No major adverse cardiovascular events (MACE) were reported during CS6-pivotal.

Table 19. Summary of Change in Fasting Lipoprotein Parameters Over Time: CS6-pivotal

Lipoprotein	Treatment group	Baseline	Month 3	Month 6	Month 12
		Mean	% CHG	% CHG	% CHG
ApoB48 (mg/dL)	PBO	9	16	10	15
	VLN	11	-75	-59	-34
Apo B (mg/dL)	PBO	69	2	-4	-6
	VLN	65	20	16	7
Apo CIII (mg/dL)	PBO	29	6	-3	-1
	VLN	31	-84	-82	-60
HDL-C (mg/dL)	PBO	17	5	5	6
	VLN	17	45	35	20
LDL-C (mg/dL)	PBO	28	7	-2	-2
	VLN	28	139	140	69
Non-HDL-C (mg/dL)	PBO	267	14	10	6
	VLN	276	-45	-39	-28
VLDL-C (mg/dL)	PBO	41	9	12	6
	VLN	40	-65	-55	-24

Source: CSR CS6-pivotal Table 14.2.3.1.1



Abbreviations: LDL-C = low-density lipoprotein cholesterol; SEM = standard error of the mean

Figure 5. Mean (±SEM) of Fasting LDL-C (mg/dL) Over Time –CS6-pivotal
Source: CSR CS6-pivotal, Figure 13

Post-prandial TG

Post-prandial responses at Baseline and during treatment (between Week 13 and Week 19) were evaluated. In the VLN group, postprandial TG AUC(0-9h) decreased from a value of 306.50 mmol*h/L at Baseline to 68.96 mmol*h/L on-treatment, which was statistically significant compared to the placebo group (p = 0.0002). Similarly, the postprandial TG AUC(0-4h) decreased from a value of 137.40 mmol*h/L at Baseline to 32.01 mmol*h/L on treatment, and was statistically significant from placebo (p < 0.0001).

Lipoprotein lipase activity

Percent change from Baseline to on-treatment post-heparin LPL activity was -31% in the VLN group as compared with -5% in the placebo group.

Reviewer Comment: This is unexpected, as one would expect a reduction in apoC-III to increase any residual LPL activity. Large variations in measurements among patients were noted by the applicant. It is unclear what significance, if any, to attribute to these results.

Dose/Dose Response

Impact of Dose Adjustment
The applicant evaluated the potential impact of dose regimen adjustment on efficacy of VLN over time. Comparisons were conducted for the 19 VLN-treated patients who completed the study with (n=13) and without (n=6) dose adjustment (change in dose interval or dose interruption) at any point in the study. All dose adjustments occurred after the primary efficacy endpoint at Month 3. In this completer population, at the Month 6 and Month 12 endpoints, patients who did not undergo dose adjustment during the study had greater mean percent

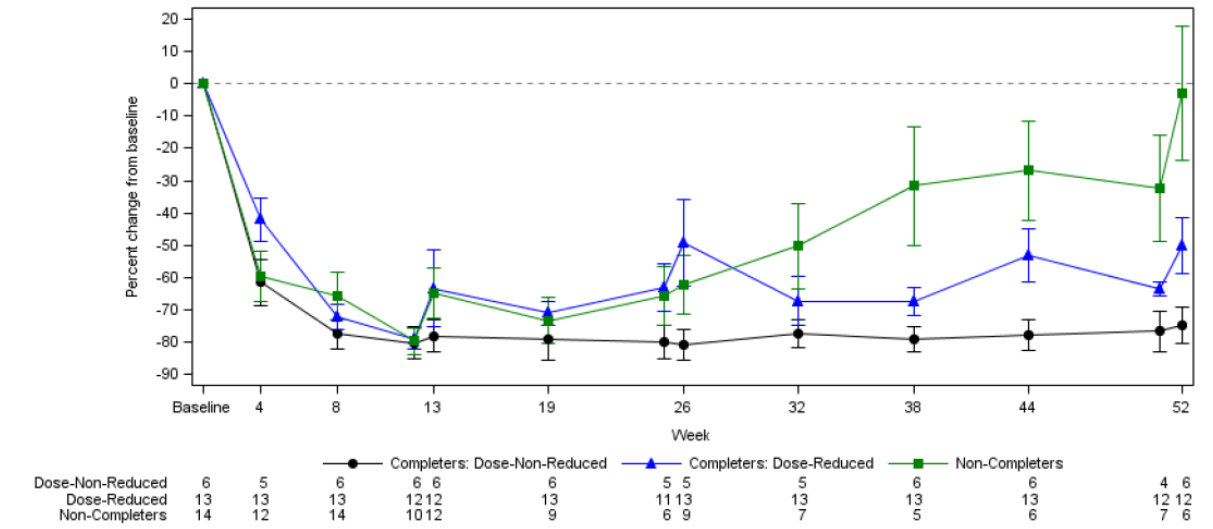
reductions in TG levels compared to patients who had the dose of VLN reduced or had a dose pause.

Table 20. Summary of Fasting TG – Completers (with or without dose adjustment/dose pause) – CS6-pivotal

Time point	Statistic	VLN 300 mg n=19 Completers	
		No Dose Adjustment/Pause n=6	With Dose Adjustment/Dose Pause n=13
Baseline	Mean (mg/dL)	2069	2520
Month 6 Endpoint	Mean (mg/dL)	413	957
	Percent Change from BL	-80	-52
Month 12 Endpoint	Mean (mg/dL)	488	1120
	Percent Change from BL	-76	-54

Source: CSR CS6-pivotal, Table 27

Mean percent change in fasting TG over time for VLN-treated patients who completed the study with or without dose adjustment and for those who withdrew early from the treatment are displayed in the figure below.



The baseline for fasting triglycerides is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 pre-dose assessment. If one of the two measurements is missing, then the other measurement will be assigned as the baseline value.
Completers: Dose-Non-Reduced include all patients who completed study treatment dosing and did not have any dose adjustment and dose pause.
Completers: Dose-Reduced include all patients who completed study treatment dosing and had dose adjustment or dose pause.
Non-Completers include all patients who were treatment early termination.

Figure 6. Mean (SEM) of Percent Change in Fasting TG over time – VLN group CS6-pivotal
Source: CSR CS6-pivotal; Figure 14.2.1.7

Reviewer Comment: Patients who remained on VLN treatment with either a dose interval change or dose pause exhibited reductions in TG. However, it is notable that only 6 of the 33 patients could maintain weekly VLN dosing for the entire study, calling into question the feasibility of 300 mg/week dosing for a chronic condition. Furthermore, the completer population may be different than non-completers due to their ability to adhere to VLN

treatment, with or without dose adjustment; therefore, extrapolating results from treatment completers to what one might expect for the typical patient taking VLN will likely overstate the average expected results.

5.2. CS16-patients with hypertriglyceridemia

Because CS16-HTG is intended to be supportive in nature, the summary below will be limited to its design and only selected efficacy analyses. From an efficacy standpoint, this trial does provide some information regarding a 300 mg biweekly dosing regimen, since a late-stage protocol amendment forced some patients to reduce their dosing frequency. This is further discussed in the clinical pharmacology review as well.

5.2.1. Study Design

Overview and Objective

The primary objective was to evaluate the efficacy of VLN as compared with placebo on percent change in fasting TG from baseline in patients with severe hypertriglyceridemia (TG ≥500 mg/dL).

Trial Design

CS16-HTG was designed as an international phase 3, double-blind, randomized, placebo-controlled study of VLN administered to patients with severe hypertriglyceridemia. There were 3 periods: a screening/diet stabilization period of up to 8 weeks, a 26-week treatment period, and a 13-week post-evaluation period. Eligible patients were randomized 2:1 to receive 300 mg VLN or placebo weekly. Stratification of patients was based on type 2 diabetes status and presence/absence of concurrent lipid-lowering therapy with a statin or fibrate. In a protocol amendment nearly 16 months after the first patient was enrolled, all patients were to have their dose reduced to 300 mg every 2 weeks at Week 13, except for those who had already completed ≥ 5 months of weekly dosing as of 27 May 2016 (Protocol Amendment 4). The primary endpoint for the study was the percent change in fasting TG from Baseline to Month 3.

Inclusion Criteria
Inclusion criteria for TG, BMI, and etiology of hypertriglyceridemia differed from CS6-pivotal. Exclusion criteria did not differ substantially from CS6-pivotal with the exception that patients with type 2 diabetes or previous history of major adverse cardiovascular event with a LDL-C >100 mg/dL or active pancreatitis within 3 months of screening were to be excluded.

Inclusion criteria CS16-HTG (selected)

- Age ≥ 18 years at time of informed consent
- Body Mass Index (BMI) ≤ 45 kg/m^2
- Stable weight (± 4 kg) for > 6 weeks prior to Screening

- Fasting TG ≥ 500 mg/dL at Screening. If the fasting TG value at Screening was < 500 mg/dL but ≥ 350 mg/dL, up to 2 additional tests could be performed in order to qualify.
- If on statin or fibrate, patients had to be on stable, labeled dose for at least 3 months prior to Screening that was not anticipated to change during the study treatment period. Patients not receiving these drugs within 4 weeks prior to Screening were also eligible.
- Fasting TG ≥ 500 mg/dL at Qualification visit (i.e. after at least 6 weeks of diet stabilization). If fasting TG was < 500 mg/dL but ≥ 350 mg/dL, up to 2 additional tests could be performed in order for patient to qualify.

Study Endpoints

Primary Endpoint
The primary endpoint was the percent change in fasting TG from Baseline as measured at the primary analysis time point (the end of Month 3), where the value was defined as the average of Week 12 (Day 78) and Week 13 (Day 85) fasting assessments.

Secondary Endpoints
Secondary endpoints included the percent of patients who achieved specific target decreases in TG, percent change in HDL-C, absolute change in fasting TG, and in patients with T2DM, change in HbA1c and HOMA-IR.

Exploratory endpoints
Exploratory endpoints included change in apolipoproteins and lipoproteins, and biomarkers of glucose metabolism

Statistical Analysis Plan

The applicant's approach to the analysis plan for CS16-HTG was generally similar to that for CS6-pivotal. The FDA statistical review does not focus on CS16-HTG, given the proposed indication; however, many of the same limitations of analyses presented for CS6-pivotal would also apply to the analyses for CS16-HTG. See the statistical review for details.

Protocol Amendments

The original protocol, dated 15 October 2014, was amended 5 times. As noted for CS6-pivotal, amendments related to platelet monitoring were implemented between April and June 2016, after the trial was well underway. Furthermore, as described above, a May 2016 protocol amendment required that patients reduce dosing from 300 mg weekly to 300 mg every 2 weeks at Week 13 (or at the time of the amendment, unless a patient had successfully completed ≥5 months of treatment), in an attempt to mitigate the risk of severe thrombocytopenia.

5.2.2. Study Results

Patient Disposition

A total of 408 patients were screened, and 114 patients were randomized 2:1 to VLN (n=76) or placebo (n=38). One of the randomized patients discontinued before receiving treatment because of failure to meet eligibility criteria.

Similar to CS6-pivotal, a higher proportion of VLN-treated patients (32%) discontinued study treatment compared to placebo-treated patients (11%). The most common reason for discontinuation of study treatment was an adverse event (20% of VLN-treated patients and 8% of placebo-treated patients; Table 21). There were 7 FCS patients included in Study CS16-HTG; none of these patients discontinued study treatment early.

Table 21. Patient disposition – CS16-HTG

	Placebo N=38	**VLN N=75**
Patients randomized and treated	38 (100)	75 (99)
Completed treatment	34 (90)	51 (67)
Early treatment discontinuation	4 (11)	24 (32)
Reason for discontinuation		
Adverse event	3 (8)	15 (20)
Voluntary withdrawal	1 (3)	3 (6)
Investigator judgement	0	1 (1)
Other	0	5 (7)

Source: CSR CS16-HTG, Table 9

Protocol Violations/Deviations

Fifteen placebo patients had a total of 24 major protocol deviations, and 24 VLN patients had a total of 41 major protocol deviations. Review of the deviations showed several instances of patients not having a platelet count within the 2-week window or being dosed without a platelet count within 14 days (placebo group 6 patients, 7 deviations; VLN group 8 patients, 11 deviations).

Table of Demographic Characteristics

The table below lists the demographic characteristics of the 113 patients treated in CS16-HTG.

Table 22. Demographic characteristics – CS16-HTG

Demographic Parameters	**Placebo N=38 n (%)**	**VLN 300 mg N=75 n (%)**
Sex		
Male	30 (79)	56 (75)

Demographic Parameters	Placebo N=38 n (%)	VLN 300 mg N=75 n (%)
Female	8 (21)	19 (26)
Age		
Mean years (SD)	53 (10)	50 (10)
Age Group		
< 17 years	0	0
≥ 17 - < 65 years	34 (89)	67 (89)
≥ 65 years	4 (11)	8 (11)
Race		
White	33 (87)	72 (96)
Black or African American	0	0
Asian	3 (8)	1 (1)
Other	2 (5)	2 (3)
Ethnicity		
Not Hispanic or Latino	37 (97)	74 (99)
BMI		
Mean (kg/m2)	30.3	31.6
Region		
United States	16 (42)	34 (45)
Rest of the World		
Canada	7 (18)	14 (19)
Europe	15 (40)	27 (36)
Other	0	0

1 Includes American Indian or Alaskan native, other race (not further defined) or multiple race
Source: CS16-HTG, adsl.xpt, CSR CS16-HTG Table 11

Reviewer Comment: Compared to patients with FCS in Study CS6-pivotal, CS16-HTG enrolled more men, patients were slightly older, BMI was greater, and a larger proportion of patients participated at sites in the United States.

Other Baseline Characteristics

Table 23. Medical history – CS16-HTG

Medical history	Placebo N=38 n (%)	VLN 300 mg N=75 n (%)
Reported history of Pancreatitis	7 (18)	10 (13)
History of type 2 DM	12 (32)	28 (37)
Coronary artery disease	4 (11)	9 (12)
Acute MI	1 (3)	0
Myocardial infarction	2 (5)	7 (9)
Coronary artery bypass	0	5 (7)
Hepatic steatosis	10 (26)	13 (17)
Cholelithiasis	5 (13)	7 (14)
Cerebrovascular accident	1 (3)	2 (3)

Source: CSR CS16-HTG Table 13, Table 14

Reviewer Comment: Compared to patients with FCS in Study CS6-pivotal, in CS16-HTG there were fewer instances of pancreatitis by medical history, more patients had type 2 DM, there were a higher proportion of patients on statins, and more patients were taking anti-platelet medications (mostly aspirin, with 7 patients on clopidogrel).

Baseline Lipid Parameters

By study design, baseline fasting TG levels were elevated. In the 7 patients with FCS in CS16-HTG, median TG levels were 2342 mg/dL at Baseline. Use of selected concomitant medications is shown in Table 25.

Table 24. Baseline lipid/lipoprotein parameters – CS16-HTG

Lipid parameters[1]	PBO N=38	VLN N=75
TG (mg/dL)		
Mean (SD)	1414 (1253)	1183 (759)
Median (P25, P75)	919 (650, 1676)	878 (679, 1553)
Apo B-48 (mg/dL) [NR: 0.15-0.83 mg/dL]	6.43	6.37
Apo C-III (mg/dL) [NR: 5-20 mg/dL]	34	35
Non-HDL-C (mg/dL)	254	232
HDL-C (mg/dL)	24	25
VLDL-C (mg/dL) [NR: 0-29 mg/dL]	63	72
LDL-C (mg/dL)	56	64

Source: CSR CS16-HTG, Table 12
1 Mean values presented unless otherwise noted. The baseline for fasting lipid measurements is defined as the average of Day 1 pre-dose assessment and the last measurement prior to Day 1 pre-dose assessment. If one of the two measurements is missing, then the other measurement is assigned as the baseline value.

Table 25. Concomitant medications – CS16-HTG

Medications	Placebo N=38 n (%)	VLN 300 mg N=75 n (%)
Fibrates	16 (42)	29 (39)
Statins	18 (47)	41 (55)
Omega-3 fish oil or ezetimibe	10 (26)	27 (36)
Platelet Aggregation inhibitors (exclude heparin)	14 (37)	27 (36)
Metformin	5 (13)	16 (21)

Source: CSR CS16-HTG, Table 15

Efficacy Results - Primary Endpoint

Table 26 presents the results for mean percent change from baseline to Month 3 endpoint in fasting TG. Patients treated with VLN for 3 months had a mean reduction in TG of 70% from Baseline compared to a mean decrease of -1% in placebo-treated patients (P<0.0001).

Table 26. Mean Percent Change from Baseline to Month 3 in Fasting TG– CS16-HTG

Month 3	Statistic	Placebo N=38	VLN 300 mg N=75
Baseline (mg/dL)	Mean (SD)	1414 (1253)	1183 (759)
Month 3 (mg/dL)	Mean (SD)	1406 (1409)	294 (245)
% Change from BL	LS Mean (95% CI)	-0.9 (-13.9, 12.2)	-71.2 (-79.3, -63.2)
Treatment Comparison			
Absolute Difference in % Change		-70.3	
95% CI		-85.4, -55.3	
p-value		<0.0001	

Source: CSR CS16-HTG; Table 18
Note: p-value of Shapiro-Wilk normality test based on observed data was <0.0001
Missing data imputed with multiple imputation

A sensitivity analysis using the Wilcoxon-rank sum testing and the Hodges-Lehmann estimator demonstrated similar findings to the primary statistical analysis with a median percent change from Baseline with VLN treatment at 3 months of -75%, and Hodges-Lehmann estimate compared to placebo of -60% (95%CI -72.5, -47.6).

The 5 patients with FCS treated with VLN in CS16-HTG experienced a similar reduction (-73%) in TG from baseline to Month 3 compared with the overall trial population.

Effect of Change in Dosing Interval

A total of 39 patients switched to biweekly treatment as a result of protocol amendment: 19 patients at the beginning of Week 13 (14 VLN, 5 placebo) and 20 patients at various timepoints from Week 13 through Week 21 (12 VLN, 8 placebo). Three additional patients adjusted their dose during the study as a result of AEs (2) and platelet count (1).

The percent reduction in TG at the end of the 26-week treatment period in the 15 patients who had their dose reduced right at Week 13 (as opposed to a later timepoint due to the timing of the amendment) was evaluated. There were no noticeable differences in the group switched at Week 13 to every other week dosing. Mean % change in TG over time is summarized in the figure below.

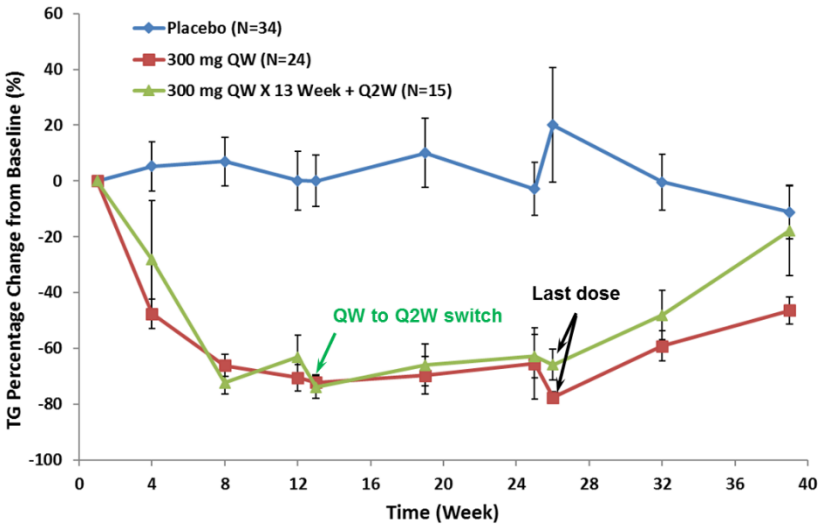


Figure 7. Mean percent change from baseline in fasting TG over time – CS16-HTG
Source: Clinical Pharmacology Reviewer Graph

Reviewer Comment: The time between switching to every other week dosing and Week 26 endpoint may not have been sufficiently long enough for new steady state in the biweekly cohort to have been achieved. Therefore, the magnitude of TG reduction in the biweekly cohort may be overestimated.

Efficacy Results - Secondary and other relevant endpoints

Since CS16-HTG is primarily intended to provide additional insight regarding the safety of VLN for this application, endpoints related to lipid/lipoprotein changes in this population are not discussed further. Directional changes in these parameters were similar to what was observed in CS6-pivotal.

HbA1c in patients with T2DM

It has been suggested that VLN improves insulin sensitivity among patients with T2DM based on a 15-week, 15-patient mechanistic study.[32] Thus, it was of exploratory interest to examine whether VLN may affect glycemic parameters among the 44 patients (39%) in CS16-HTG who had a medical history of type 2 diabetes. At baseline, the mean HbA1c in this subgroup was 7.1% in the placebo group and 7.2% in the VLN group. At Month 3, HbA1c had increased 0.1% in the VLN group and had decreased 0.1% in the placebo group (p=0.27). At Month 6, HbA1c had increased 0.4% in the VLN group and had decreased 0.2% in the placebo group (p=0.03). The applicant states that an imbalance in baseline antidiabetic therapy with 70% of patients in the placebo group being on insulin, compared to 27% of patients in the VLN group, may have contributed to the observed differences.

[32] Digenio A, et al. *Diabetes Care* 2016;39:1408-1415.

Reviewer Comment: In CS6-pivotal, there was a small number of patients with type 2 diabetes at baseline (4 in placebo, 6 in VLN). Small numerical increases in HbA1c in VLN patients with type 2 diabetes were noted: 0.3% at Month 3, 0.1% at Month 6, and 0.1% at Month 12. The difference from placebo was +0.4%, +0.1%, and +0.4% at Month 3, 6, and 12, respectively.

Additional Analyses Conducted on the Individual Trial

SAEs suggestive of acute pancreatitis were adjudicated by the Pancreatitis Adjudication Committee. The table below provides a summary of adjudicated pancreatitis events in CS16-HTG.

Overall, there were 3 placebo-treated patients that reported 7 pancreatitis events and 1 VLN-treated patient reporting 1 pancreatitis event on or after the first dose of study drug. The event in the VLN-treated patient (and in one of the placebo-treated patients) occurred more than 90 days after last dose.

Table 27. Adjudicated Acute Pancreatitis Events – CS16-HTG

	PBO N=38		VLN N=75	
	n (%)	Events	n (%)	Events
Patients with an adjudicated event post-first dose[1]	**3 (8)**	**7**	**1 (1)**	**1**
Timing of events by treatment period category				
Patients with any on-treatment adjudicated event[2]	3 (8)	5	0	0
Patients with any after-treatment adjudicated event[3]	0	0	0	0
Patients with any post-follow-up adjudicated event[4]	1 (3)	2	1 (1)	1

Source: CSR CS16-HTG, Table 48
1 Post-dose defined as all acute pancreatitis events that occurred after the first dose of the study drug through the end of the study
2 An on-treatment event was defined as any adjudicated event starting on or after the first dose of the Study Drug to the last dose of the Study Drug +28 days.
3 An after-treatment event was defined as any adjudicated event starting on or after the last dose of the Study Drug +29 days to the last dose of the Study Drug +90 days.
4 A post-follow up event was defined as any adjudicated event starting after the last dose of the study drug +90 days

5.3. Study CS7-FCS Open-Label Extension

5.3.1. Study Design

Overview and Objective

This is an ongoing Phase 3 open-label extension study of VLN to further evaluate the safety and efficacy of VLN in patients with FCS.

Trial Design

In this ongoing, single-arm, open-label extension study, there are 3 groups of patients being enrolled:

- Patients with FCS who completed the parent study CS6-pivotal
- Patients with FCS who completed in the parent study CS16-HTG
- Patients with FCS who did not participate in either study (i.e., "new" patients)

Patients who had participated in a parent protocol had up to 2 weeks to complete qualification assessments. Patients who had not participated in a parent protocol entered an 8-week screening and qualification period, including a diet stabilization period of at least 6 weeks, unless the sponsor approved earlier treatment because the patient had already been on an appropriate diet before the screening period.

Approximately 70 patients are planned to receive 300 mg VLN weekly for 52 weeks. Following the 52 weeks, patients have the option to continue dosing for an additional 52 weeks or enter a 13-week post-treatment evaluation period.

The same DSMB and Adjudication Committees for CS6-pivotal reviewed and/or adjudicated the data for CS7-OLE.

Landmark Dates

First patient enrolled	23 December 2015
Initial Data cut-off date for NDA	6 January 2017
4-month safety update cut-off date	31 August 2017

Eligibility Criteria

The Inclusion and Exclusion criteria were originally the same as CS6-pivotal. After a protocol amendment (July 6, 2016), on-study testing of LPL activity to establish study eligibility was removed "to avoid the production of heparin-induced anti-platelet antibodies."

Reviewer Comment: In the applicant's evaluation of mechanism for VLN-induced thrombocytopenia, no antibodies associated with heparin-induced thrombocytopenia (i.e., anti-PF4 IgG) were detected among 25 patients from CS6-pivotal, CS7-OLE, and CS16-HTG who developed thrombocytopenia <100,000/mm^3, including 3 patients with FCS with platelet count <25,000/mm^3. LPL activity has been included in recent diagnostic algorithms for FCS, especially when determining the pathogenicity of novel genetic variants.

Study Assessments

Efficacy and safety endpoints were similar to CS6-pivotal. Efficacy evaluations included changes in TG, other lipid/lipoproteins, and signs and symptoms of FCS such as change in abdominal pain and adjudicated pancreatitis event rate. Safety assessments included changes in platelet values, local injection site reactions, flu-like reactions, and clinical chemistries. Depending on a given analysis, the definition of "baseline" varied depending on whether the patient had

participated in a parent trial, the reference time of interest (e.g., parent study baseline or open-label study baseline), the availability of information in the parent study (e.g., abdominal pain and other PROs were not administered in CS16-HTG), and the assessment of interest (e.g., baseline platelet count was calculated differently than baseline lipid measurements). Details are presented if necessary for interpretation.

Protocol Amendments

The original protocol, dated 28 August 2015, was amended 6 times as of the data cut-off date of 6 January 2017. Protocol Amendment 4, dated 6 June 2016, modified platelet monitoring. Additional amendments that applied to all patients included removal of *on-study* LPL activity testing as a possible method for qualification for patients who had not participated in CS6-pivotal, and a second re-challenge for patients who had required dose interruptions for low platelet counts was no longer allowed.

Reviewer Comment: After the data cut-off date for this NDA submission, a 7th amendment was added to the ongoing CS7-OLE trial after a new 15-day report was submitted. A patient treated with VLN for the first time in CS7-OLE experienced a platelet count <25,000/mm^3. Amendment 7 (dated 7 April 2017) included weekly monitoring of platelet count and added an exclusion criterion for patients with baseline platelet counts below the lower limit of normal. This amendment also allowed a medical history of LPL activity ≤20% of normal; however, testing of LPL activity was not to be performed to confirm eligibility for the study.

5.3.2. Study Results

Patient Disposition

Results are described for the following groups of patients:

- Treatment-naïve group: combination of patients who received placebo during the parent studies, CS6-pivotal and CS16-HTG, and "new" patients who did not participate in either parent study
- CS6-VLN: Patients who received VLN in CS6-pivotal and enrolled in CS7-OLE after successfully completing that trial
- CS16-VLN: Patients who received VLN in CS16-HTG and enrolled in CS7-OLE after successfully completing that trial

At the time of the initial NDA submission's data cut-off for CS7-OLE, there were 29 patients enrolled. The treatment-naïve group comprised 17 patients from the placebo group in CS6-pivotal and 1 patient from the placebo group in CS16-HTG. There were no patients who hadn't participated in a parent trial. Three (10%) of these 29 patients had discontinued due to an adverse event before data cut-off.

With the 4-month safety update, using a data cut-off of 31 August 2017, an additional 31 patients had enrolled for a cumulative total of 60 patients. The treatment-naïve group

cumulatively comprised 43 patients: 30 from the placebo group in CS6-pivotal, 2 from the placebo group in CS16-HTG, and 11 "new" patients. Twelve (20%) of these 60 patients had discontinued due to either an adverse event or voluntary withdrawal: 7 (16%) from the 43 treatment-naïve patients and 5 (36%) from the 14 who had been treated with volanesorsen in CS6.

Table 28. Patient Disposition – CS7-OLE

	Initial Cut-off Date 6 January 2017				4-month safety update 31 August 2017 (cumulative)			
	Treatment-naïve n (%)	CS6-VLN n (%)	CS16-VLN n (%)	Total n (%)	Treatment-naïve n (%)	CS6-VLN n (%)	CS16-VLN n (%)	Total n (%)
Patients Enrolled	18	11	0	29	43	14	3	60
Patients Dosed	18 (100)	11 (100)	0	29 (100)	43 (100)	14 (100)	3 (100)	60 (100)
Patients continuing treatment	16 (89)	10 (91)	0	26 (90)	36 (84)	9 (64)	3 (100)	48 (80)
Patients who discontinued VLN	2 (11)	1 (9)	0	3 (10)	7 (16)	5 (36)	0	12 (20)
Main reason for discontinuation of VLN								
Adverse event	2 (11)	1 (9)	0	3 (10)	4 (9)	4 (29)	0	8 (13)
Voluntary withdrawal	0	0	0	0	3 (7)	1 (7)	0	4 (7)

Source: CSR CS7-OLE, Table 8; 120-day safety update Table 3

Reviewer Comment: As of the cut-off date of 31 August 2017, only 9 (27%) of the 33 patients treated with VLN in CS6-pivotal remained on VLN treatment.

Protocol Violations/Deviations

Four of the initial 29 CS7-OLE patients experienced at least 1 major protocol deviation during the study; 3 patients received VLN without having a platelet assessment within 14 days; this occurred for each of these patients 2 or 3 times during the study. All patients continued in the study. Similar protocol deviations were observed in the 4-month safety update.

Demographic Characteristics

The demographics and baseline characteristics were similar between treatment-naïve patients and patients exposed to VLN in parent trials. In the treatment-naïve group, mean baseline TG levels were elevated at 2288 mg/dL (initial data cut-off). Baseline abdominal pain in the treatment-naïve group was low and similar to results observed in CS6-pivotal (initial data cut-off).

Other Baseline Characteristics

Approximately 80% of patients had on-study genetic testing that was consistent with FCS. There were 8 (13%) patients that did not have confirmatory on-study genetic testing – 7 of these patients were enrolled in CS6-pivotal and were discussed previously in Section 5.1.2. Of the 11 patients enrolled for the first time in CS7 (CS7-new), all had confirmatory genetic testing.

Table 29. Number (%) of patients in CS7-OLE that met on-study genetic confirmation for FCS (4-month safety update cutoff)

	Treatment-naive			CS6-VLN N=14 n (%)	CS16-VLN N=3 n (%)	Total N=60 n (%)
	CS7-new N=11 n (%)	CS16-PBO N=2 n (%)	CS6-PBO N=30 n (%)			
Confirmed	11 (100)	2 (100)	23 (77)	11 (79)	1 (33)	48 (80)
Not Confirmed	0	0	5 (17)	2 (14)	1 (33)	8 (13)
Missing	0	0	2 (7)	1 (7)	1 (33)	4 (7)

Source: Response to FDA IR, submitted 15 March 2018, Table 1

Efficacy Results - Primary Endpoint

At the time of the initial data cut-off, the number of patients in CS7-OLE with TG values at the primary efficacy timepoint was very small (10 in the treatment-naïve group and 4 in the CS-VLN group). Changes in TG were directionally favorable and were generally consistent with changes observed in CS6-pivotal.

In the 4-month safety update, the applicant reported 2 SAEs adjudicated as pancreatitis events in CS7-OLE, one patient "on treatment" and one patient "off treatment" (after treatment discontinuation due to an AE).

6. Review of Safety

Summary of Safety

The primary trial to describe the safety of VLN in patients with FCS is CS6-pivotal, a 1-year, randomized, placebo-controlled study in 66 adult patients with FCS. The safety of VLN was supplemented by an ongoing open-label extension study in patients with FCS, CS7-OLE, and a 6-month trial in a non-FCS population of patients with severe hypertriglyceridemia (CS16-HTG). In general, the safety profile observed with VLN use in the pivotal trial was confirmed in the supplementary studies. The safety issues identified with VLN include a high rate of discontinuation due to adverse events, thrombocytopenia and risk of bleeding, injection site reactions, hypersensitivity/immunogenicity, flu-like reactions, renal-related adverse events, and liver enzyme elevations.

In CS6-pivotal, a total of 33 patients with FCS were exposed to VLN; the average exposure in the VLN group was 267 days (35 doses) compared to 352 days (49 doses) in the placebo group. The lower treatment duration and smaller number of injections in VLN-treated patients reflect a higher number of discontinuations and dose adjustments due

to adverse events. Only 1 (3%) placebo-treated patient discontinued during the 52-week treatment period compared with 14 (42%) VLN-treated patients; 9 (27%) of the VLN-treated patients discontinued due to an adverse event. Of the 19 VLN-treated patients who completed the trial, only 6 patients remained on weekly dosing of VLN.

The primary safety concern in this application is VLN-induced thrombocytopenia and risk of bleeding. In CS6-pivotal, the average platelet count at baseline was 221,000/mm^3 (normal 140,000/mm^3 to 400,000/mm^3). Patients treated with VLN exhibited a decline in platelet count of approximately 30%, on average, within the first 6 months. However, central tendency measures alone do not fully describe the clinically significant platelet reductions observed with VLN treatment. In the VLN development program, individual patients experienced rapid, severe decreases in platelet counts, illustrated by an analysis of nadir platelet count any time post baseline dose (Table 30).

In CS6, a higher proportion of patients treated with VLN than placebo developed thrombocytopenia (76% vs. 27%), defined as platelet count less than the lower limit of normal (LLN) (<140,000/mm^3). Similarly, a greater proportion of patients in the VLN arm had platelet nadirs below standard thresholds defining greater severity of thrombocytopenia. Although the applicant contends that patients with FCS have significant variability in platelet count and thrombocytopenia, it is notable that in this randomized placebo-controlled trial of patients with FCS, the incidence of thrombocytopenia was substantially higher among VLN-treated patients than placebo-treated patients, and no subjects in the placebo arm had a platelet count below 100,000/mm^3.

Table 30. Number (%) of patients with nadir platelet counts meeting threshold value at any time post-baseline (Phase 3 trials)

	CS6-pivotal		CS16-HTG		CS7-OLE
Number of patients with platelet count at any time	**PBO N=33 n(%)**	**VLN N=33 n(%)**	**PBO N=38 n(%)**	**VLN N=75 n(%)**	**VLN Treatment-naïve N=43**
Platelet count <140,000/mm^3	9 (27)	25 (76)	6 (16)	30 (40)	33 (76)
Platelet count <100,000/mm^3	0	18 (55)	1 (3)	9 (12)	22 (51)
Nadir platelet count post-baseline					
100,000 to <140,000/mm^3	9 (27)	7 (21)	5 (13)	21 (28)	11 (26)
75,000 to <100,000/mm^3	0	6 (18)	1 (3)	6 (8)	16 (37)
50,000 to <75,000/mm^3	0	9 (27)	0	2 (3)	3 (7)
25,000 to <50,000/mm^3	0	1 (3)	0	1 (1)	2 (5)
<25,000/mm^3	0	2 (6)	0	0	1 (2)

Source: Response to IR submitted 18 Dec 2017, Table 4, Table 8; 4-month safety update, 28 December 2017, Table 14.3.4.1.8d.1

The shaded rows in the table above highlight 7 (4.6%) of 151 patients exposed to 300 mg/week in the phase 3 program that had a platelet count <50,000/mm^3. This table does not include 1 additional patient with FCS from the phase 2 trial, CS2, who had a nadir platelet count

<50,000/mm^3, nor does it include the most recent report submitted (after the 4-month safety update) of a patient in CS7-OLE with a platelet nadir of 17,000/mm^3.

In aggregate, 9 patients in the VLN development program have had a platelet count <50,000/mm^3. The timing of onset to platelet count <50,000/mm^3 has been highly variable, ranging from 51 to 300 days. Because of the small size of the database, data to predict which patients might be at risk or when severe thrombocytopenia might occur – which would possibly allow for guidelines for monitoring based on duration of treatment exposure – is lacking.

In the cases where follow-up information was available, platelet count recovered with discontinuation of study drug with or without additional treatment (6 of the 9 patients received steroids, including 1 patient who received steroids and IVIG). In 3 of the 9 cases, elongating the VLN dosing interval did not stabilize platelet count and VLN was ultimately discontinued. Two of the 9 patients were rechallenged with weekly VLN dosing: one patient maintained platelet counts above 100,000/mm^3, whereas the other had a second platelet nadir <50,000/mm^3 resulting in discontinuation of VLN. There is insufficient information, at this time, to predict who is likely to tolerate a rechallenge with VLN treatment.

In the VLN clinical program, no serious bleeding events have occurred, although a higher proportion of VLN-treated patients have experienced bleeding events. In CS6-pivotal, 16 (49%) VLN-treated patients reported 45 events versus 4 (12%) placebo-treated patients with 5 events, as defined by the MedDRA Hemorrhage SMQ. Even after excluding bleeding events at the injection site or lab-related adverse event terms, a higher proportion of VLN-treated patients (36%) had clinical bleeding events compared to placebo (6%); the most frequent clinical bleeding events were epistaxis and petechiae. Most of the bleeding events occurred at a platelet count above 75,000/mm^3, suggesting that other factors such as platelet dysfunction may contribute to the risk of bleeding. Investigations into the mechanism underlying VLN's effect on platelet, including platelet function, have been inconclusive.

The applicant has noted that after enhanced platelet monitoring and dose adjustments were instituted in CS6-pivotal, no further discontinuations (other than 1 discontinuation due to "Investigator decision" for platelet count 93,000/mm^3) occurred with biweekly monitoring, and that no patient subsequently met the criteria for discontinuation with the revised dose adjustment and platelet monitoring program. However, the experience of this subset of VLN-treated patients in CS6-pivotal, who had all tolerated treatment for more than 6 months before the enhanced safety measures were implemented (n=20), may not be representative of treatment-naïve patients treated with VLN. Furthermore, discontinuations due to platelet declines have continued in the ongoing open-label study CS7-OLE (despite implementation of enhanced monitoring), including 4 patients with platelet counts below 50,000/mm^3, one of whom experienced a platelet nadir of 17,000/mm^3 despite <u>weekly</u> platelet monitoring.

Across the phase 3 controlled trials, treatment-emergent adverse events were higher in VLN-treated versus placebo-treated patients. In CS6-pivotal, 32 (97%) VLN-treated patients reported a total of 985 TEAEs during the study compared with 31 (94%) patients and 227 TEAEs in the placebo group. In CS16-HTG, 74 (99%) VLN-treated patients reported 2045 TEAEs compared with 34 (90%) placebo patients who reported 194 TEAEs.

Adverse events at the injection site were the most common TEAEs reported in the phase 3 trials. In CS6-pivotal, 79% of VLN-treated patients experienced 497 individual events at the injection site, compared to no events in placebo-treated patients. In CS16-HTG, 65 (87%) of VLN-treated patients had 1055 injection site reactions compared to 3 (8%) of subjects in the placebo group with 8 events. Only 1 VLN-treated patient in the pivotal trial discontinued due to an injection site reaction associated with fatigue. A higher percentage of patients in CS16-HTG discontinued due to injection site reactions. Skin discoloration was noted at the injection site for 20 to 30% of patients administered VLN; for several patients, this discoloration persisted and had not resolved at the time of data cut-off.

Serious hypersensitivity reactions occurred in two non-FCS patients treated with VLN (one case of anaphylaxis requiring emergent treatment and one serum sickness requiring hospitalization and steroids). The onset of symptoms of serum sickness was coincident with the emergence of high-titer anti-VLN antibodies (ADA). Both patients recovered with discontinuation of VLN and supportive care. No serious hypersensitivity events have occurred in the FCS population, although one patient with FCS developed itching and erythema involving the whole body surface, leading to treatments with steroids, antihistamines, and eventually cyclosporine. It is reasonable to anticipate that additional potentially serious hypersensitivity reactions may occur in FCS patients treated with VLN, if approved.

Positive anti-VLN antibodies occurred in approximately a third of VLN-treated patients in CS6-pivotal. The onset of ADA positivity was approximately 6 months, and patients generally remained positive for the remainder of the study. It did not appear that changes in ADA titers had an impact on TG levels or platelet counts. Two patients with FCS discontinued VLN treatment due to systemic symptoms (chills and sweating; chills, fever, and myalgias). Both patients were positive for ADA at the time symptoms were reported. The contribution of ADA to these events and serious cases of hypersensitivity cannot be definitively ruled out.

VLN treatment was associated with flu-like reactions, other constitutional symptoms, and increases in the inflammation biomarker hsCRP. Two VLN-treated patients in CS6-pivotal and one patient in CS7-OLE discontinued treatment due to fatigue; there were also higher proportions VLN-treated patients (≥8%) reporting constitutional symptoms such as fatigue, myalgia, arthralgia, diarrhea, nausea, and abdominal pain as an AE compared to placebo-treated patients in both CS6-pivotal and CS16-HTG.

Small imbalances in renal-related events were noted in CS6-pivotal with VLN treatment – transient increase in creatinine (50% increase from baseline or ≥0.3 mg/dL) occurred in 4

(12%) VLN patients and no placebo-treated patients. No serious renal events were reported. However, given the small safety database and the association of renal adverse events (e.g. glomerulonephritis) with other antisense oligonucleotides, routine monitoring for these types of events may be warranted.

Two (3%) non-FCS patients treated with VLN in CS16-HTG met liver-related stopping criteria for elevated ALT and AST values >8x ULN. One case was confounded by alternative etiologies. In the other case, following 4 doses of VLN treatment, liver enzymes increased >8x ULN, the subject's bilirubin remained normal, no alternative etiology could be discerned, and liver enzymes normalized with study drug discontinuation. Given the temporal association with VLN-treatment, a causal association cannot be excluded. No patient treated with VLN met the laboratory criteria for Hy's law (i.e., ALT or AST greater than 3x ULN accompanied by total bilirubin greater than 2x ULN).

VLN has not been studied in pediatric patients; therefore, its safety in this population is unknown. It is of concern, given the expected timing of symptom onset with FCS, that off-label use in children and adolescents may occur.

During the review cycle, the applicant submitted revised draft labeling, including new dosing and administration instructions for VLN based on weight and absolute platelet count. The revised proposed label recommends platelet count monitoring at least every two weeks, and adjustment of dose frequency after an initial 3 months based on body weight. The applicant submitted post hoc analyses of patients treated with VLN who completed clinical trials CS6 and CS16 to justify the regimen, but has not evaluated the new strategy prospectively in a clinical trial (see the clinical pharmacology review for further details). It is unknown if this strategy will adequately mitigate the risk of thrombocytopenia and serious bleeding events.

6.1. Safety Review Approach

Phase 1 and 2 trials were screened for safety signals that may not have been identified in the phase 3 program. Serious adverse events from ongoing blinded clinical trials in other patient populations were also reviewed and included in this review if applicable.

The following additional safety topics were reviewed based on identification of a signal during pre-market investigation of VLN, from information known about anti-sense oligonucleotides in general, or standard safety review practices:

- Thrombocytopenia
- Injection-site reactions
- Flu-like reactions
- Hypersensitivity

- Immunogenicity
- Renal-related adverse events
- Liver-related adverse events

The safety population in all clinical trials was defined as randomized patients who received at least 1 dose of study drug. Patients were analyzed in the treatment group according to the actual treatment they received.

6.2. Review of the Safety Database

The primary data for review of VLN safety was from CS6-pivotal, the 1-year placebo-controlled trial in patients with FCS. Supportive safety data was provided in CS16-HTG, a 26-week placebo-controlled trial in patients with high TG. Seven patients with FCS were enrolled in CS16-HTG. All eligible patients with FCS completing treatment in these parent studies could elect to enroll in an open-label extension study, CS7-OLE.

Following reports of serious thrombocytopenia, the applicant submitted a protocol amendment for CS16-HTG that changed the dosing interval from weekly to every other week at the beginning of Week 13 for all patients except those who had already received ≥ 5 months of treatment at the time of the amendment. The applicant presented safety data by VLN dosing cohort of weekly (n=25), biweekly post-Week 13 (n=50), and total (n=75). For analysis purposes, the applicant included patients who received 9 or fewer doses in the last 3 months, including those who discontinued treatment early, in the biweekly post-Week 13 cohort. Thus, the applicant has combined three different types of patients in the "biweekly post-Week 13 cohort": (1) patients who required a dose reduction "for-cause" (e.g., adverse events); (2) patients who had missed a certain number of doses (for whatever reason) or discontinued treatment prematurely; and (3) patients who were tolerating weekly VLN but had their dose reduced by protocol amendment (at variable times from Week 13 through Week 21). Use of information that occurred after randomization (i.e., tolerability) to define this cohort complicates the interpretation of comparisons between the "biweekly post-Week 13" and "weekly" dosing cohorts presented by the applicant. Since the primary purpose of CS16-HTG was to supplement the safety profile of VLN compared to placebo, this review focuses primarily on the comparison of all VLN-treated patients ("VLN total") with placebo, recognizing that the VLN group comprises a mixture of exposure to 300 mg weekly and 300 mg every other week.

The applicant provided pooled analyses from CS6-pivotal and CS16-HTG termed a Placebo-Controlled Phase 3 Group. A second pooled analysis was conducted on 4 studies, two Phase 2 studies (CS2-DF and CS4-DM) and two Phase 3 studies (CS6-pivotal and CS16-HTG) to form a Placebo-Controlled Phase 2 and Phase 3 Group. Although the Phase 3 study designs share a placebo-controlled period and starting dose of VLN (300 mg weekly), the duration of treatment where these factors were consistent is small (12 weeks). CS6-pivotal and CS16-HTG had key differences that may impact the types and frequency of events, including different patient populations, treatment durations (1 year versus 26 weeks), and treatment allocation (1:1 vs. 2:1). These same considerations apply to the Placebo-Controlled Phase 2 and Phase 3 Group

pool. In this reviewer's opinion, pooling did not provide additional information that cannot be gleaned from review of the individual trial safety data. Therefore, this review does not present pooled safety data.

6.2.1. Overall Exposure

At the time of the initial data cutoff date of January 18, 2017, a total of 126 patients were exposed to VLN in the phase 3 program, including 56 patients with FCS. Three additional patients with FCS were exposed to VLN in the dose-finding Phase 2 study CS2-DF. In the 4-month safety update (data cutoff of 31 August 2017), an additional 25 treatment-naïve patients with FCS have enrolled in CS7-OLE, for a total of 81 patients with FCS exposed to at least one dose of VLN in the Phase 3 program.

Table 31 provides the number of patients exposed to either VLN or placebo in the phase 3 clinical trials. Treatment exposure separated by individual clinical trial immediately follows the table.

Table 31. Phase 3 Safety Population

Phase 3 Safety Database			
Clinical Trial Groups	VLN Initial data cut-off 18 January 2017	Placebo Initial data cut-off 18 January 2017	VLN 4-month safety update 31 August 2017 (Incremental)
Controlled trials conducted for FCS indication **CS6-PIVOTAL**	33	33	0
All other than controlled trials conducted for this indication[1] **CS7-OLE**	18 (treatment-naïve)	NA	25 (treatment-naïve)
Controlled trials conducted for other indications **CS16-HTG**	75 (5 with FCS)	38 (2 with FCS)	0

[1] VLN treatment naïve
Phase 2 study CS2 included 3 patients with FCS treated with 300 mg VLN for 13 weeks and are not included in the table above

Study CS6-pivotal

A summary of study drug exposure and treatment duration for Study CS6-pivotal is provided in Table 32. In general, exposure to VLN was less than placebo due to discontinuations for adverse events or laboratory values. Up to the primary efficacy timepoint of Month 3, study drug exposure was well-maintained for both treatment groups but decreased for VLN after Month 3 due to a higher number of early terminations, dose adjustments, and dose interruptions due to

adverse events or abnormal platelet values. Only 6 of 33 VLN-treated patients completed the 52 weeks of treatment without a reduction in dose frequency or treatment pause in study CS6-pivotal.

Table 32. Summary of Study Drug Exposure – CS6-pivotal

	PBO N=33 n (%)	VLN N=33 n (%)
Days of Treatment		
Mean (SD)	352 (35)	267 (113)
Range	163 to 379	57 to 372
N (%) of subjects		
≥3 months	33 (100)	31 (94)
≥6 months	32 (97)	24 (73)
≥ 9 months	32 (97)	21 (64)
≥ 12 months	21 (64)	8 (24)
Number of Injections		
Mean (SD)	49 (6)	35 (15)
Range	24 to 53	5 to 53
N (%) of subjects		
1-8 doses	0	1 (3)
9-12 doses	0	1 (3)
13-25 doses	1 (3)	9 (27)
26-51 doses	19 (58)	20 (61)
>51 doses	13 (39)	2 (6)
Patients with Dose Frequency Adjustment and/or Dose Interruption	6 (18)	17 (52)
Patients with Biweekly Dosing Frequency	*0*	*10 (30)*
Reason for Biweekly Dosing		
Adverse event	0	2 (6)
Lab value	0	8 (24)
Patients with Dose Interruption	6 (18)	12 (36)
Reason for Dose Interruption		
Adverse event	4 (12)	9 (27)
Lab value	1 (3)	5 (15)
Other	1 (3)	1 (3)

Source: CSR CS6-pivotal, Table 57; Response to IR (SD 18), Table 9, submitted 15 December 2017

Reviewer Comment: The patients listed as "Other" as reason for dose interruption have reported adverse events – Subject (b) (6) *placebo group "Other" had ongoing AE retroorbital headache and diplopia, Subject* (b) (6) *in the VLN group the reason recorded for dose pause are "AE" for arthralgia and "Other" text includes "PI decided to stop study drug injection due to worsening of platelet reduction and arthralgia".*

CS16-HTG

The mean duration of treatment was 160 and 136 days for the placebo and VLN groups, respectively (Table 24). Patients that met the criteria for inclusion in the 300 mg weekly cohort had an average treatment duration of 175 days, whereas those that met the criteria for the

post-Week 13 biweekly cohort[33] had a mean treatment duration of 116 days.

Table 33. Summary of Study Drug Exposure - CS16-HTG

	Placebo N=38	VLN N=75
Days of Treatment		
Mean (SD)	160 (46)	136 (63)
Range	1 to 204	1 to 193
N (%) of subjects		
1-8 doses	3 (8)	16 (21)
9-12 doses	1 (3)	1 (1)
13-25 doses	17 (45)	39 (52)
26 doses	16 (42)	19 (25)
Patients with Dose Frequency Adjustment and/or Dose Interruption		
Patients with Biweekly dosing adjustment	13 (34)	29 (39)
Reason for Biweekly Dosing		
Per protocol amendment	13 (34)	26 (35)
Lab value	0	1 (1)
Adverse event	0	2 (3)
Patients with Dose Interruption/Pause	3	10 (13)
Reason for dose interruption/pause		
Adverse event	2 (5)	6 (8)
Lab value	1 (3)	4 (5)

Source: CSR CS16-HTG, Table 42

Reviewer Comment: By study design, treatment duration in CS16-HTG is less than CS6-pivotal.

Study CS7-OLE

At the time of the initial data cutoff, the mean treatment duration in the CS7-OLE for the treatment-naïve group was 109 days. For patients who had received VLN in CS6 before enrolling in CS7-OLE, the mean treatment duration was 473 days (includes both trials). Additional treatment exposure with the 4-month safety update is described in the table below.

[33] Patients who received 9 or fewer doses in the last 3 months, including those who discontinued early and did not meet the minimum dose requirement for the weekly cohort, were assigned to the biweekly post-Week 13 cohort according to the Statistical Analysis Plan.

Table 34. Summary of treatment exposure – CS7-OLE

	Initial cut-off		4-month safety update Cumulative (31 August 2017)		
	Treatment-naïve N=18 n (%)	CS6-VLN N=11 n (%)	Treatment-naïve N=43	CS6-VLN N=14	CS16-VLN N=3
Days of Treatment					
Mean (SD)	109	473	162	647	507
Range	1 to 337	361 to 742	1 to 564	385 to 971	414 to 625
N (%) of subjects					
≥3 months	10 (56)	11 (100)	35 (81)	14 (100)	3 (100)
≥6 months	3 (17)	11 (100)	20 (47)	14 (100)	3 (100)
≥ 9 months	1 (6)	11 (100)	12 (28)	14 (100)	3 (100)
≥ 12 months	0	11 (100)	6 (14)	14 (100)	3 (100)
≥ 18 months	0	2 (18)	1 (2)	10 (71)	1 (33)
≥ 24 months	0	1 (9)	0	5 (36)	0
Number of Injections					
Mean (SD)	15 (10)	54 (19)	22 (15)	66 (22)	30 (4)
Range	1 to 36	28 to 99	1 to 70	34 to 116	27 to 34
N (%) of subjects					
1-8 doses	5 (28)	0	7 (16)	0	0
9-12 doses	3 (17)	0	7 (16)	0	0
13-25 doses	7 (39)	0	15 (35)	0	1 (33)
26-52 doses	3 (17)	7 (64)	12 (28)	3 (21)	2 (67)
53-67 doses	0	2 (18)	2 (5)	8 (57)	0
68-80 doses	0	1 (9)	0	1 (7)	0
81-93 doses	0	0	0	0	0
94-103 doses	0	1 (9)	0	0	0
>103 doses	0	0	0	2 (14)	0

Source: CSR CS7-OLE, Table 14.3.1.1.2 Exposure includes information from Parent-study CS6-pivotal and CS7-OLE

Reviewer Comment: When considering the safety results from CS7-OLE, it will be important for the reader to keep in mind the differences in exposure between the dosing cohorts.

Using information from the 4-month safety update, there are 18 (30%) patients in CS7-OLE on weekly VLN (average treatment duration 26 weeks), although 1 of those patients was on a dose pause as of 31 August 2017.

Of the 33 patients originally randomized to VLN treatment in CS6-pivotal, 14 elected to enroll in the open-label trial, only 1 of whom continues to receive weekly VLN treatment in CS7-OLE (Patient (b) (6)).

Half of the patients in CS7-OLE are receiving VLN every other week; the most common reason for dose adjustment was lab values.

Table 35. Summary of VLN dosing frequency – CS7-OLE (4-month safety update)

	Treatment-naïve N=43 n (%)	CS6-VLN N=14 n (%)	CS16-VLN N=3 n (%)	Total N=60 n (%)
Number (%) receiving VLN 300 mg/week	15 (35)	1 (7)	2 (67)	18 (30)
Number (%) receiving VLN 300 mg every other week	21 (49)	8 (57)	2 (67)	31 (52)
Number (%) discontinued treatment	7 (16)	5 (36)	0	12 (20)

Source: Response to FDA IR submitted 15 March 2018

6.2.2. Relevant characteristics of the safety population:

The patients contributing to the full analysis set and safety set in CS6-pivotal are identical. Therefore, the reader is referred to Section 5.1.2 for further details regarding the patient population in CS6-pivotal. Because the safety database is supplemented by CS16-HTG, the relevant characteristics of the safety populations in CS6-pivotal and CS16-HTG are listed in the table below for comparison.

Table 36. Baseline characteristics of the study population CS6-pivotal and CS16-HTG

	CS6-pivotal N=66	CS16-HTG N=113
Demographics		
Male (%)	46	76
Age (years)	46	51
White (%)	80	93
Metabolic characteristics		
Weight (kg)	70	94
BMI (kg/m2)	25	31
TG (mg/dL) median	1985	884
LDL-C (mg/dL)	28	61
VLDL-C (mg/dL)	41	64
apoB (mg/dL)	67	98
apoB48 (mg/dL)	10.2	6.4
apoC-III (mg/dL)	30	35
Medical history		
Type 2 diabetes (%)	15	35
Pancreatitis (%)	76	29
Thrombocytopenia (%)	5	0
Cardiac disorders (system organ class)	20	34
Concomitant Medications		
Fibrate	49	40
Statin	21	52
Other lipid modifying agents (fish oil derived, ezetimibe)	29	33
Platelet aggregation inhibitors (excl. heparin)	20	36

Source: CSR CS6-pivotal, Table 13-18; Table 14.1.1.2, 14.1.3.1, 14.1.4 3b, CSR CS16-HTG, Table 11, 12, 14, 14.1.3.1

Reviewer Comment: Differences noted between the two study populations are expected given the different patient population studied. Study CS16-HTG was mostly male, slightly older, with numerically higher BMI, lower median TG, higher levels of LDL-C, VLDL-C, and apoB, higher incidence of cardiac disorders, diabetes, and statin use compared to patients with FCS. The CS16-HTG population is reflective of a much larger population of individuals with hypertriglyceridemia. Hypertriglyceridemia in this population may be the result of multiple factors including underlying genetic predisposition which manifests with acquired risk factors such as obesity and/or diabetes.

6.2.3. **Adequacy of the safety database:**

The safety database for this application is small, due in part to the rarity of the FCS population. The applicant was strongly encouraged, before phase 3 was initiated, to bolster the safety database by increasing the size of studies investigating VLN in other patient populations, especially since the applicant was contemplating development of VLN for the more common severe hypertriglyceridemia (i.e., non-FCS, TG >500 mg/dL) at the time. In response, the applicant conducted a small (n=113), 6-month, placebo-controlled trial in patients with severe hypertriglyceridemia. The strengths of the safety database include the placebo-controlled design and the 1-year treatment duration in the indicated treatment population, with additional longer-term exposure in the open-label extension. Significant safety risks have emerged within this small population that will be described in following sections. It is possible, especially given the size of the database, that additional safety signals may emerge or be more clearly characterized with additional exposure in patients with FCS.

A weakness of the phase 3 program was the reliance on a single dosing regimen and the multiple changes to the dosing regimen and platelet monitoring, in response to VLN-associated thrombocytopenia, when the phase 3 trials were well underway. Changes to dosing frequency and monitoring occurred after the pivotal trial was fully enrolled (date of change May 2016), after the last patient in the pivotal trial had received the last dose of study drug (date of change April 2017), and yet again 5 months after NDA submission (date of proposed change submitted January 24, 2018).

There are no prospective trials planned to evaluate efficacy and safety of the new dosing proposals.

These factors limit the reviewer's capacity to accurately characterize the safety profile of the VLN with the alternatively proposed dosing regimens.

6.3. Adequacy of Applicant's Clinical Safety Assessments

6.3.1. Categorization of Adverse Events

All adverse events were coded using MedDRA v19.1. A treatment-emergent adverse event (TEAE) was defined as any event starting or worsening on or after the first dose of Study Drug. This is also referred to as an on-study event.

The applicant classified treatment-emergent AEs into 3 periods: on-treatment, after-treatment, and post-follow up periods based on the start date of the event:

- On-treatment period: first dose → last dose + 28 days
- After-treatment period: last dose +29 days → last dose + 90 days
- Post-study period: after last dose + 90 days

Reviewer Comment: For this safety review, TEAEs are reported as occurring any time after first dose of study drug, unless a specific time period is noted.

6.4. Safety Results

6.4.1. Deaths

There were no deaths in the VLN clinical development program.

6.4.2. Serious Adverse Events

Serious adverse events (SAEs) were defined as any AE that resulted in death, was life-threatening, required inpatient hospitalization or prolonged a current hospitalization, caused persistent or significant disability/incapacity, or was a congenital anomaly/birth defect in the offspring of a patient who received study drug. In addition, any event that required intervention to prevent one of these outcomes could be considered an SAE, but this was at the judgment of the investigator.

Narratives, as well as relevant datasets, adjudication packages, and CRFs were reviewed for these events. These events will be further described, where applicable in submission-specific safety topics (i.e. serious events related to thrombocytopenia are discussed in Section 6.5.1 Platelet-Related Safety Concerns)

SAEs in CS6-pivotal

In the CS6-pivotal trial, a total of 14 treatment-emergent SAEs were reported in 12 patients during the study; seven (21%) patients in the VLN-treated group and 5 (15%) in the placebo-treated group. Two VLN-treated patients in CS6-pivotal experienced an SAE of thrombocytopenia leading to treatment discontinuation (Table 37).

Table 37. Treatment-emergent Serious Adverse Events – CS6-pivotal

Preferred Term	PBO N=33 n (%)	VLN N=33 n (%)
Any treatment-emergent SAE	**5 (15)**	**7 (21)**
Thrombocytopenia	0	2 (6)
Abdominal pain	1 (3)	1 (3)
Cyst	0	1 (3)
Cholangitis	0	1 (3)*
Drug-induced liver injury	0	1 (3)*
Ankle fracture	0	1 (3)
Dehydration	0	1 (3)
Liver function test abnormal	1 (3)	0
Colitis ischemic	1 (3)	0
Pancreatitis acute	2 (6)	0

Source: CSR CS6-pivotal Table 63.
*Occurred in the same patient (with the same date of onset).

SAEs CS7-OLE

In the ongoing CS7-OLE, no SAEs were noted at the initial data cut-off; however, with the 4-month safety update, 5 SAEs were reported, including 1 treatment-naïve VLN-treated patient who experienced an SAE of thrombocytopenia with platelet count <25,000/mm^3 that led to study discontinuation. The other SAEs reported in the 4-month safety update - diverticulitis and urinary tract infection, myalgia, and clavicle fracture were reviewed; the SAEs of thrombocytopenia and myalgia will be further discussed in future relevant sections.

SAEs in CS16-HTG

A similar proportion of patients in the placebo and VLN group reported SAEs (Table 38). All narratives for VLN-treated patients were reviewed.

Table 38. Serious TEAE by Preferred Term – CS16-HTG

Preferred Term	PBO N=38 n (%)	VLN N=75 n (%)
Any treatment-emergent SAE	**4 (11)**	**8 (11)**
Pancreatitis acute	2 (5)*	1 (1)
Small intestinal obstruction	0	1 (1)
Carotid artery stenosis	0	1 (1)
Hemiparesis	0	1 (1)
Hypertensive crisis	0	1 (1)‡
Non-cardiac chest pain	0	1 (1)‡
Vertigo	0	1 (1)‡
Peripheral arterial occlusive disease	0	1 (1)
Serum sickness	0	1 (1)
Ulna fracture	0	1 (1)

Preferred Term	PBO N=38 n (%)	VLN N=75 n (%)
Cholelithiasis	1 (3)*	0
Pancreas infection	1 (3)*	0
Ileus paralytic	1 (3)†	0
Pancreatitis relapsing	1 (3)†	0
Asthma	1 (3)	0

Source: CSR CS16-HTG; Table 50
*,†,‡ Events denoted with the same symbol occurred in the same patient (not necessarily concordant in time)

SAEs in Phase 2 trial: CS2-DF

There were 3 VLN-treated patients in CS2-DF who experienced 6 SAEs: arterial restenosis, femoral arterial stenosis, cellulitis, hematoma, serum sickness-like reaction, and pancreatitis acute; no SAEs were documented in the placebo group.

Reviewer Comment: To date, in the VLN clinical program, there are two reports of SAEs coded as serum-sickness or serum-sickness like reaction that required steroid treatment in patients treated with study drug. One of the patients developed high positive ADA titer during the event which suggests VLN-induced serum sickness. Further discussion of this case may be found in Section 6.5.1 (Immunogenicity/Hypersensitivity).

6.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

The phase 3 protocols (CS6-pivotal, CS7-OLE, CS16-HTG) had pre-specified stopping rules for liver enzyme elevations, renal function, and platelet counts. In addition, dose adjustments, including dose interruptions and/or decreasing the dose frequency, were allowed for safety and tolerability, but these adjustments were not to occur unless necessary prior to the primary analysis time point (Month 3).

- Adverse Events Leading to Treatment Discontinuation

CS6-pivotal
In CS6-pivotal, 9 (27%) VLN-treated patients permanently discontinued treatment due to an adverse event (Table 39). In contrast, no placebo-treated patients discontinued treatment because of an AE. Five patients discontinued treatment for adverse events related to platelet count (2 SAEs "thrombocytopenia", 3 non-SAEs "decreased platelet count"). One patient discontinued due to persistent erythema, which had extended to the "whole body surface," requiring steroid treatment (narrative follows table).

Table 39. Discontinuations due to treatment-emergent adverse events – CS6 pivotal

Subject	VLN Dose[1]	Days of AE	Total number of doses before DC VLN	Day of Last Dose of VLN[1]	Day of Last Visit	Reported Verbatim Term	Comment
(b) (6)	300 mg/QWk	51-166	19	127	341	thrombocytopenia	Platelet count <25,000/mm^3
	300 mg/QWk	257-292	37	256	461	thrombocytopenia	Platelet count <25,000/mm^3
	300 mg/QOW	316-358	25	317	413	decreased platelet	This patient had not received VLN from Study Day 156-303 due to epistaxis, gingival bleeds. Restarted on VLN 300 mg QOW on Study Day 303
	300 mg/QWk	127-230	22	190	358	Low platelet count	Patient had 3 dose interruptions, prior to discontinuation of study treatment due to plt count
	300 mg/QWk	85-142	16	106	388	Reduced platelet count	
	300 mg/QWk	95-102	14	94	176	Severe Fatigue	Patient had experienced 8 separate AEs of fatigue before the final AE report of fatigue that led to study treatment discontinuation. Fatigue followed administration of study drug, typically lasting 1 to 2 days
	300 mg/QWk	22-ongoing	13	85	359	Pain, burning, edema, erythema, loss of sensitivity, hyperpigmentation, depression in skin at injection site; Prostration; fatigue	Hyperpigmentation and skin depression at injection site ongoing. Other symptoms resolved by Study Day 116.
	300 mg/QOW	274-277	33	274	413	Chills, sweating	Patient was on every other dosing at the time of AE leading to DC due to persistent abdominal injection site induration. Patient experienced two previous episodes of chills, sweating on Study Day 247, Day 260 before treatment DC

Subject	VLN Dose[1]	Days of AE	Total number of doses before DC VLN	Day of Last Dose of VLN[1]	Day of Last Visit	Reported Verbatim Term	Comment
(b) (6)	300 mg/QWk	96-112	14	92	358	Erythema extended to whole body surface	Experienced 2 additional events of erythema requiring steroids, cyclosporine. See narrative in this section

[1] VLN dosing regimen at time of the event. No placebo-treated patients discontinued due to an AE.
Source: CS6-pivotal adae.xpt; CSR narratives

- Patient (b) (6) was a 58-year-old male with diagnosis of hypertriglyceridemia with confirmed low LPL activity (genetic mutation consistent with FCS not confirmed). Patient was on fenofibrate, simvastatin, and ezetimibe, and was randomized to VLN 300 mg weekly. On Study Day 72, the patient began treatment with cetirizine for swelling and itching at the injection site. Weekly dosing continued, the patient's 14th dose of VLN was administered on Study Day 92. On Study Day 93, the patient was switched to topical clobetasol for rash prophylaxis, and the concomitant medications levothyroxine, Co-Diovan, fenofibrate, and simvastatin/ezetimibe were stopped. On Study Day 96, the patient experienced "erythema extended to whole body surface" and "itching" of moderate intensity that prompted the patient to go to emergency room; the patient was discontinued from VLN treatment. On Study Day 105, the patient had no symptom relief, a dermatologist was consulted, and the patient was started on methylprednisolone and desloratidine for these symptoms. The erythema apparently resolved on Study Day 112, but a second event of whole body erythema of moderate intensity was reported approximately a week later, on Study Day 118. The dose of methylprednisolone was increased and another antihistamine started. Symptoms resolved on Study Day 127 but recurred on Study Day 168 (abdominal erythema) and the patient began treatment with cyclosporine. The erythema resolved on unknown date. The patient was negative for anti-VLN antibodies.

Reviewer Comment: Event of erythema and itching significant for persistence, multiple recurrences after drug discontinuation, and need for dermatology referral, steroids and cyclosporine to resolve. No additional laboratories or skin biopsy to evaluate these events were provided.

Two VLN-treated patients discontinued due to fatigue (Patient (b) (6), Patient (b) (6)) in CS6-pivotal, and one patient in CS7-OLE (see narrative below); a slightly higher proportion of VLN-treated patients reported fatigue as an AE compared to placebo-treated patients. In this reviewer's opinion, this suggests VLN does not favorably affect the incidence of fatigue in patients with FCS.

CS7-OLE

In CS7-OLE, 2 out of 29 patients discontinued VLN due to an AE as of the initial data cutoff. With the 4-month safety update, a cumulative total of 8 (13%; 4 treatment-naïve and 4 CS6-VLN) of 60 patients had discontinued VLN due to an adverse event. The most common AE leading to discontinuation was thrombocytopenia (n=5), one of which was an SAE for a platelet count <25,000/mm^3, which prompted an amendment to the ongoing CS7-OLE study to monitor platelets weekly for all patients in ongoing VLN trials (patient (b) (6)). Three patients in CS7-OLE discontinued treatment due to constitutional symptoms: chills and myalgia resulting in hospitalization (1 patient (b) (6)) – further described in 6.5.3; fatigue and myalgia (1 patient (b) (6)); and blurred vision, vomiting, headache, nausea, abdominal pain, contusion (1 patient). The narrative of the patient discontinuing due to fatigue and myalgia is summarized below.

- Patient (b) (6), a 54-year-old white male enrolled in CS6-pivotal and was randomized to VLN 300 mg/weekly. The patient completed CS6-pivotal without any dose interruptions or elongation of dosing frequency. During CS6-pivotal, he reported moderate neck and lumbar disc disorder (Study Day 53) and myalgia on Study Day 56. These events were all ongoing at the time of initiation into CS7-OLE. On the first day of CS7-OLE, the patient reported fatigue (not reported during CS6-pivotal). The patient continued to experience myalgia and fatigue until discontinuation. He took pain medication as needed. The patient discontinued VLN treatment in CS7-OLE due to the events of myalgia and fatigue. At time of study drug discontinuation, the patient had received 48 doses of VLN in CS6-pivotal and 18 doses in CS7-OLE.

CS16-HTG

Fifteen (20%) patients in the volanesorsen group discontinued study treatment because of TEAEs compared to 3 (8%) patients in the placebo group. Among the 15 VLN-treated patients who discontinued due to an AE, 9 were for adverse events at the injection site, 1 for thrombocytopenia (Patient (b) (6)), 2 as a result of meeting a liver-related stopping rule (elevated transaminases), and 1 for serum sickness. Another two patients discontinued under the category "Other." However, review of these patients noted that 1 patient had thrombocytopenia <50,000/mm^3 (b) (6)) and 1 patient met the renal-stopping rules (proteinuria; (b) (6)) at the time of study drug discontinuation. The patients who met renal- or liver-related stopping rules and platelet count <50,000/mm^3 are described in the relevant safety sections.

Phase 2 CS2-DF

A total of 6 VLN-treated patients discontinued treatment due to an AE. One of the patients discontinued due to the SAE of serum sickness-like reaction, the remainder discontinued due to adverse reactions at the injection site (n=3), fatigue (n=1), and a diagnosis of mononucleosis (n=1).

- Adverse Events/Laboratory Values Leading to Dose Interruptions and/or Change in

Dosing Interval

In CS6-pivotal, a total of 6 (18%) placebo-treated patients and 17 (52%) VLN-treated patients had either a change in dosing interval (i.e. weekly to biweekly) and/or dose interruption. Of the 17 VLN-treated patients, 5 had both a dose interruption and a change in the dosing interval. None of the placebo-treated patients had a change in dosing interval.

Adverse events or laboratory values leading to elongation of dosing interval in the VLN-treated group (n=10) included injection site induration and discoloration in 1 patient, thrombocytopenia in 1 patient, and low platelets (not reported as an AE) in 8 patients. Treatment interruptions occurred in 12 VLN-treated patients due either to an AE (mostly related to injection site reactions or platelet related event) or low platelet counts that were not reported as adverse events. It is unclear whether there was a consistent approach among investigators regarding when to report platelet-related abnormalities as adverse events.

Of the 17 VLN-treated patients with a dose interruption or change in dosing interval, 4 eventually discontinued study treatment permanently (3 due to AEs, 1 "voluntary withdrawal"), 5 eventually resumed weekly dosing, 1 patient did not restart dosing in CS6-pivotal but enrolled in CS7-OLE, and the remaining 7 continued treatment every other week.

6.4.4. Treatment Emergent Adverse Events and Adverse Reactions

CS6-pivotal

The following table lists the TEAEs that occurred in ≥5% of patients (in either arm) in study CS6-pivotal sorted by frequency. While the proportion of patients in the placebo and VLN-treatment groups who experienced a TEAE is similar, the number of events is considerably higher in the VLN group than the placebo group (VLN: 985 events in 32 patients; PBO: 227 events in 31 patients). Most events in the VLN-treated patients were related to adverse events at the injection site. Events at the injection site were also the most frequently reported TEAEs in CS16-HTG.

Table 40. Treatment-emergent adverse events ≥5% in either treatment group – CS6-pivotal

Preferred Term	PBO N=33	VLN N=33	PBO	VLN
	n (%)	n (%)	#Events	#Events
Any TEAE	*31 (94)*	*32 (97)*	227	985
Injection site erythema	1 (3)	25 (76)	1	235
Injection site pain	3 (9)	15 (46)	25	63
Platelet count decreased	1 (3)	10 (30)	1	12
Abdominal pain	7 (21)	9 (27)	11	13
Injection site pruritus	0	8 (24)	0	69
Fatigue	3 (9)	7 (21)	3	23
Headache	5 (15)	7 (21)	8	10
Injection site discoloration	0	7 (21)	0	23
Injection site induration	0	7 (21)	0	36

Preferred Term	PBO N=33	VLN N=33	PBO	VLN
	n (%)	n (%)	#Events	#Events
Injection site swelling	2 (6)	7 (21)	15	24
Erythema	3 (9)	6 (18)	3	8
Nausea	2 (6)	6 (18)	3	12
Asthenia	3 (9)	5 (15)	3	7
Diarrhea	2 (6)	5 (15)	3	11
Epistaxis	0	5 (15)	0	7
Injection site bruising	0	5 (15)	0	15
Injection site edema	0	5 (15)	0	19
Myalgia	1 (3)	5 (15)	1	10
Nasopharyngitis	7 (21)	5 (15)	10	8
Vomiting	3 (9)	5 (15)	6	7
Arthralgia	0	4 (12)	0	10
Diabetes mellitus	0	4 (12)	0	4
Injection site reaction	0	4 (12)	0	15
Pain in extremity	1 (3)	4 (12)	1	5
Petechiae	0	4 (12)	0	4
Thrombocytopenia	0	4 (12)	0	5
Hypertension	0	3 (9)	0	3
Influenza like illness	0	3 (9)	0	3
Injection site hypoesthesia	0	3 (9)	0	3
Injection site pallor	0	3 (9)	0	37
Injection site warmth	0	3 (9)	0	9
Pruritus	2 (6)	3 (9)	4	5
Rash	1 (3)	3 (9)	1	3
Urticaria	0	3 (9)	0	6
Abdominal pain upper	4 (12)	2 (6)	4	3
Chills	0	2 (6)	0	6
Constipation	0	2 (6)	0	2
Creatinine renal clearance decreased	0	2 (6)	0	2
Hyperhidrosis	0	2 (6)	0	5
Hypoesthesia	1 (3)	2 (6)	1	2
Injection site dryness	0	2 (6)	0	13
Injection site hematoma	0	2 (6)	0	4
Injection site urticaria	0	2 (6)	0	64
Malaise	0	2 (6)	0	3
Nasal congestion	1 (3)	2 (6)	1	2
Neck pain	0	2 (6)	0	2
Edema	1 (3)	2 (6)	2	2
Paraesthesia	0	2 (6)	0	2
Sinusitis	1 (3)	2 (6)	1	2
Somnolence	0	2 (6)	0	2
Urinary tract infection	3 (9)	2 (6)	4	4
Vaginal hemorrhage	0	2 (6)	0	2
Back pain	4 (12)	1 (3)	6	1
Cough	4 (12)	1 (3)	6	11
Chest pain	2 (6)	1 (3)	3	1
Gastroenteritis	3 (9)	1 (3)	4	1

Preferred Term	PBO N=33	VLN N=33	PBO	VLN
	n (%)	n (%)	#Events	#Events
Hemoglobin decreased	2 (6)	1 (3)	2	1
Influenza	3 (9)	1 (3)	3	1
Upper respiratory tract infection	2 (6)	1 (3)	3	1
Flatulence	2 (6)	0	3	0
Hypernatremia	2 (6)	0	2	0
Oropharyngeal pain	3 (9)	0	4	0
Pain	2 (6)	0	3	0
Acute pancreatitis	2 (6)	0	2	0
Viral infection	2 (6)	0	2	0

Source: CSR CS6-pivotal Table 14.3.1.3.1d

Reviewer Comment: Excluding TEAEs at the injection site, events occurring among >10% of patients and with higher incidence in the VLN group include decreased platelet count, abdominal pain, erythema, asthenia, fatigue, headache, nausea, vomiting, myalgia, arthralgia, pain in extremity, petechiae, thrombocytopenia, epistaxis, and diabetes mellitus. A similar pattern of TEAEs was also noted among VLN-treated patients in CS16-HTG (*Table 41 below).*

Reactions at the injection site were evaluated separately as an adverse event of interest and are discussed further in Section 6.5.2.

Four patients with FCS treated with VLN reported AEs of diabetes mellitus in CS6-pivotal compared to none in the placebo treated group. Review of the narratives provided for these patients suggests 1 of these events, in this reviewer's opinion, was related to VLN: steroid-induced diabetes secondary to treatment for platelet reduction. Regarding the other cases, one of the patients had a worsening of existing diabetes while hospitalized for severe dehydration secondary to diarrheal illness, and the other two patients had elevated baseline fasting glucose levels (135 mg/dL and 140 mg/dL, respectively) and HbA1c levels at pre-diabetes thresholds at baseline (5.7% and 6.4%); neither of the latter two patients started antidiabetic medications.

Table 41. TEAE Occurring in ≥5% of patients (excluding events at the injection site) – CS16-HTG

Preferred Term	PBO N=38	VLN N=75	PBO	VLN
	n (%)	n (%)	#Events	#Events
Any TEAE	***34 (90)***	***74 (99)***	***194***	***2045***
Back pain	4 (11)	12 (16)	7	14
Nasopharyngitis	5 (13)	12 (16)	6	17
Red blood cell sedimentation rate increased	4 (11)	11 (15)	4	12
Thrombocytopenia	2 (5)	10 (13)	2	11
Abdominal pain	1 (3)	10 (13)	1	14
Diarrhea	4 (11)	10 (13)	11	23
Fatigue	4 (11)	9 (12)	15	15
Arthralgia	0	9 (12)	0	10
C-reactive protein increased	0	8 (11)	0	10

Preferred Term	PBO N=38	VLN N=75	PBO	VLN
	n (%)	n (%)	#Events	#Events
Pain in extremity	1 (3)	7 (9)	1	7
Nausea	1 (3)	7 (9)	1	10
LDL-C increased	0	7 (9)	0	7
Headache	4 (11)	7 (9)	5	17
Pyrexia	2 (5)	7 (9)	2	10
Myalgia	0	6 (8)	0	11
Asthenia	2 (5)	5 (7)	2	13
Vomiting	1 (3)	5 (7)	1	5
Depression	0	5 (7)	0	6
Anemia	2 (5)	4 (5)	3	5
Dizziness	2 (5)	4 (5)	2	4
Hepatic enzyme increased	0	4 (5)	0	4
Diabetes mellitus	0	4 (5)	0	4
Erythema	0	4 (5)	0	5
Dry mouth	0	4 (5)	0	4
Upper respiratory tract infection	2 (5)	4 (5)	2	4
Bronchitis	3 (8)	4 (5)	3	4
Platelet count decreased	2 (5)	3 (4)	3	3
Type 2 diabetes mellitus	2 (5)	2 (3)	2	2
Cough	3 (8)	2 (3)	3	2
Pain	2 (5)	2 (3)	2	2
Upper abdominal pain	3 (8)	2 (3)	3	2
Acute pancreatitis	2 (5)	1 (1)	3	1
Hot flush	2 (5)	1 (1)	2	1
Influenza	2 (5)	1 (1)	2	1
Vertigo	2 (5)	1 (1)	2	1
Actinic keratosis	2 (5)	0	8	0

Source: CSR CS16-HTG Table 14.3.1 31b

CS7-OLE

In CS7-OLE, the most common treatment-emergent adverse events were related to injection site reactions. Beyond injection site reactions, the most common TEAEs were nasopharyngitis, abdominal pain, nausea, platelet count decreased, arthralgia, fatigue, and headache. These events were similar to those observed in CS6-pivotal.

Table 42. TEAE ≥10% overall (excluding injection site reactions) – CS7-OLE (4-month safety update)

	Treatment-naïve N=43	CS6-VLN N=14	CS16-VLN N=3	Overall N=60
	n (%)	n (%)	n (%)	n (%)
Patients with any TEAE	**40 (93)**	**14 (100)**	**2 (67)**	**56 (93)**
Nasopharyngitis	9 (21)	2 (14)	0	11 (18)
Abdominal pain	6 (14)	4 (29)	0	10 (17)
Nausea	6 (14)	4 (29)	0	10 (17)
Platelet count decreased	7 (16)	2 (14)	0	9 (15)

	Treatment-naïve N=43	CS6-VLN N=14	CS16-VLN N=3	Overall N=60
	n (%)	n (%)	n (%)	n (%)
Arthralgia	6 (14)	1 (7)	0	7 (12)
Fatigue	4 (9)	3 (21)	0	7 (12)
Headache	4 (9)	3 (21)	0	7 (12)
Diarrhea	4 (9)	1 (7)	1 (33)	6 (10)
Dizziness	4 (9)	2 (14)	0	6 (10)
Pyrexia	4 (9)	2 (14)	0	6 (10)
Thrombocytopenia	5 (12)	1 (7)	0	6 (10)
Urinary tract infection	3 (7)	3 (21)	0	6 (10)

Source: 4-month safety update Table 14 3.1.9b

6.5. Analysis of Submission-Specific Safety Issues

6.5.1. Platelet-related Safety Concerns

Non-clinical Findings
In the non-clinical program, thrombocytopenia-related mortalities in monkeys were noted at ≥12 mg/kg/week or approximately equivalent to clinical exposure levels. For further information on the non-clinical studies and platelet effects, refer to the non-clinical review.

Approach to monitoring/assessing platelet-related effects in VLN clinical trials
In phase 2 trials, platelets were obtained during the treatment period every 2 weeks during the first month, then every 4 weeks, and at the end of the follow-up period. A confirmed platelet count less than 75,000/mm^3 required permanent discontinuation of drug.

In the initial proposal for phase 3 trials, the applicant proposed excluding patients with platelet counts less than the lower limit of normal. However, in the EOP2 meeting discussion, the applicant was encouraged to minimize exclusion criteria since it could be expected that patients with FCS may use VLN, if approved, regardless of platelet count; therefore, safety data should be obtained in the setting of a clinical trial where monitoring can be optimized.

In the original protocols for the phase 3 trials, platelet count was assessed every 4 to 6 weeks. No exclusion criterion for baseline platelet levels was included; however, patients with a history of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at screening would be excluded. Patients could be on oral anticoagulants if the dose had been stable for at least 4 weeks prior to screening. The table below describes the changes to platelet monitoring and VLN dosing as the clinical safety signal emerged. Major changes occurred with notification of two VLN-treated patients with platelet count <25,000/mm^3 (Amendment 6/updates). At that time, study CS6-pivotal was fully enrolled and 49 patients were still actively taking study drug (29 placebo and 20 VLN).[34] Major changes included (1) increasing platelet assessment to every 2 weeks; (2) patients could not be dosed

[34] Response to FDA IR, submitted 15 December 2017

until a platelet value from within the last 14 days was reviewed, as well as the trend in values; (3) platelet counts from 75,000/mm^3 to 100,000/mm^3 resulted in change to the dosing regimen to 300 mg every other week (or 150 mg every week, but this dose was never used); and (4) the threshold for stopping drug permanently or temporarily was increased from 50,000/mm^3 to 75,000/mm^3. In February 2017, the FDA received a 15-day safety report of a patient treated in CS7-OLE who had a platelet nadir <25,000/mm^3 ((b) (6)) despite platelet monitoring every 2 weeks. This case led to an amendment to intensify platelet monitoring further (weekly labs) and permanent discontinuation of study drug as well as steroid treatment for platelet count <50,000/mm^3.

Table 43. Changes to VLN protocol: platelet monitoring and treatment

	Original Protocol (June 2014)	Amendment 4 (April 2016)	Amendment 5 (May 5, 2016)	Amendment 6/updates (May 27, 2016; June 6, 2016; June 28, 2016)	Amendment 7 (April 2017) Applied to CS7-OLE
Frequency of routine platelet monitoring	4-6 wks	3-4 wks Blood sent to central and local lab Uninterpretable values rechecked within 1 wk	Any uninterpretable values to be rechecked and determined not to meet stopping rule before dosing	Every 2 weeks PLT count and trend to be reviewed before dosing	Every week
Increased monitoring	PLT reduction ≥30% AND PLT<75,000; or bleeding	Any significant reduction or PLT <75,000		Weekly: 75,000-140,000 2 to 3 days: 50,000-75,000 Daily: <50,000	
Dose Pause	PLT<50,000 AND NO major or clinically relevant bleeding[35]			<75,000 AND NO major or clinically relevant bleeding	
Permanent discontinuation	PLT<50,000 AND major or clinically relevant bleeding.			PLT<25,000 or <75,000 on QOW dosing or <75,000 AND major or clinically relevant bleeding	PLT<50,000
Dose Rechallenge	Up to 2 times once PLT ≥100,000 with		Following rechallenge, PLT checked every	1 Rechallenge only if patient had been on weekly dosing and	

[35] Major bleeding defined as fatal bleeding, symptomatic bleeding in critical area or organ (i.e. intracranial), bleeding causing fall in hemoglobin level of ≥20 g/L, or leading to transfusion of ≥2 units. Clinically relevant, non-major bleeding was defined as any of the following: multiple-source bleeding, spontaneous hematoma >25 cm2, excessive wound hematoma (not injection site related), macroscopic hematuria (spontaneous or lasting >24 hours if associated with an intervention), spontaneous rectal bleeding, epistaxis, gingival bleeding, hemoptysis, hematemesis, bleeding after venipuncture >5 minutes.

	medical monitor consultation		week until stable	PLT≥100,000 with medical monitor consultation	
Dose Interval				CS6-pivotal: QOW when PLT 75,000-100,000 or with rechallenge	

Baseline Platelet Values

Given the reported platelet variability in patients with FCS, the baseline platelet count in CS6-pivotal was defined as the average of all assessments prior to the first dose of Study Drug.

The averaged baseline level of platelets in CS6-pivotal was 228,000/mm^3 and 215,000/mm^3 in the placebo and VLN groups, respectively. The mean baseline level of platelets in CS16-HTG was 236,000/mm^3 in both placebo and VLN groups.

Reviewer Comment: The proposed strategy for mitigating the risk of thrombocytopenia in labeling includes contraindicating use of VLN in patients with pre-treatment platelet count <140,000/mm^3, but the proposed dosing algorithm (Table 44) allows continued treatment of VLN in patients who have an on-treatment platelet count <140,000/mm^3. The applicant proposes to recommend permanent discontinuation of treatment for platelet count <25,000/mm^3.

Table 44. Proposed Dose Adjustment for VLN

	Dose Adjustments		
PLT Level	**Body Weight < 70 kg**	**Body Weight ≥ 70 kg**	**PLT Monitoring**
Normal (≥140k)	Starting dose: weekly for 3 months Biweekly thereafter	Weekly	Biweekly
100k-140k	Biweekly	Weekly	Biweekly
75k-100k	Biweekly	Biweekly	Weekly
50k-75k	Pause, resume biweekly when ≥100		Twice per week until stable
<50k	Pause, resume biweekly when ≥100		Daily until stable
<25k	Discontinue Waylivra*		Daily until stable

* For any patient dose paused or discontinued due to severe thrombocytopenia, the benefits and risks of returning to treatment should be carefully considered and a hematologist should be consulted prior to resuming treatment.

Source: Applicant submission 24 January 2018

Platelet values over time

As shown in the figure below, platelets decreased over time for the patients in the VLN group compared to those in the placebo group during CS6-pivotal. Declines in platelet count of approximately 30% occurred during the first 6 months of the trial; there were 3 patients in CS6-pivotal who had severe decreases in platelet count to less than 50,000/mm^3. Similar patterns for platelet reductions were observed in CS16-HTG, with 1 patient having a platelet count <50,000/mm^3. These patients, along with five additional patients with platelet reductions to

<50,000/mm^3, will be discussed in further detail later in this Section.

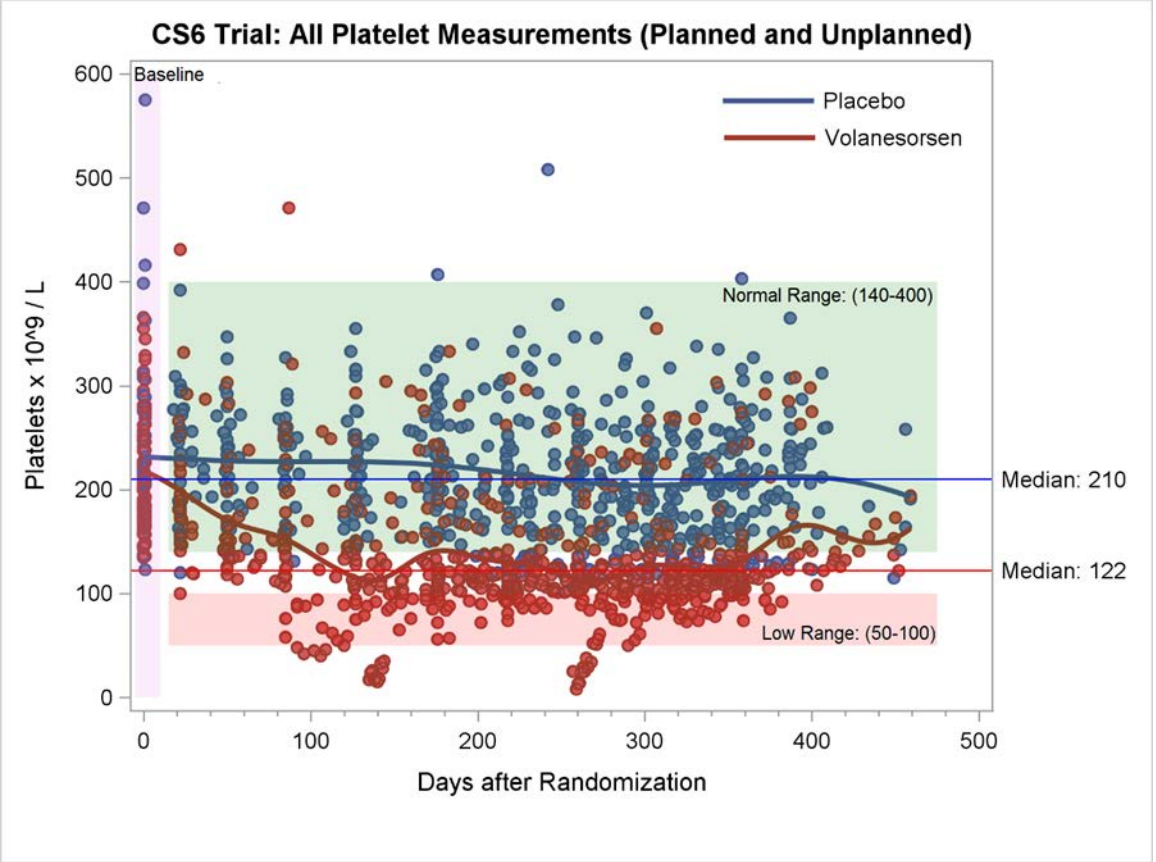


Figure 8. Plot of Platelet Count Over Time – CS6-pivotal
Note: Dots indicate individual patients' platelet counts with spline curves that approximate the average platelet count through time for each treatment
Source: Dr. Andraca-Carrera

Categorical changes in platelet count

Reviewer Comment: Note that the following analyses in Table 45 and Table 46 do not include the most recently reported case of thrombocytopenia - platelet count <25,000/mm^3 in the ongoing open-label study (patient (b) (6)), since the case was submitted after these analyses were conducted. This latest case is discussed in Table 47 and in the accompanying narratives.

Categorical changes in platelet count at any time post-baseline are described in the table below for patients in CS6-pivotal and CS16-HTG. At baseline, only 3 patients in CS6-pivotal had baseline platelet levels between 100,000 and 140,000/mm^3. No patients in CS16-HTG had platelet counts below 140,000/mm^3 at baseline.

A higher proportion of patients treated with VLN exhibited categorical declines in platelet count compared to patients treated with placebo in both CS6-pivotal and CS16-HTG (Table 45).

Reviewer Comment: The applicant contends that patients with FCS have significant variability in platelet count, suggesting that significant thrombocytopenia may occur as part of the natural history of the disease. However, in this 52-week, randomized placebo-controlled trial of patients with FCS, the incidence of thrombocytopenia was substantially higher among VLN-treated patients than placebo-treated patients (76% vs. 27% had any platelet count <140,000/mm^3, and 55% vs. 0% had any platelet count <100,000/mm^3).

Table 45. Number (%) of patients with nadir platelet counts meeting threshold value at any time post-baseline: CS6-pivotal, CS16-HTG, CS7-OLE treatment-naive

	CS6-pivotal		CS16-HTG		CS7-OLE
Number of patients with platelet count at any time post-baseline	**PBO N=33 n (%)**	**VLN N=33 n (%)**	**PBO N=38 n (%)**	**VLN N=75 n (%)**	**VLN Treatment-naïve N=43 n (%)**
Platelet count <140,000/mm^3	9 (27)	25 (76)	6 (16)	30 (40)	33 (77)
Platelet count <100,000/mm^3	0	18 (55)	1 (3)	9 (12)	22 (51)
Nadir platelet count post-baseline					
100,000 to <140,000/mm^3	9 (27)	7 (21)	5 (13)	21 (28)	11 (26)
75,000 to <100,000/mm^3	0	6 (18)	1 (3)	6 (8)	16 (37)
50,000 to <75,000/mm^3	0	9 (27)	0	2 (3)	3 (7)
25,000 to <50,000/mm^3	0	1 (3)	0	1 (1)	2 (5)
<25,000/mm^3	0	2 (6)	0	0	1 (2)

Source: Response to IR submitted 18 Dec 2017, Table 4, Table 8; 4-month safety update, 28 December 2017, Table 14.3.4.1.8d.1

Reviewer Comment: In the original NDA submission, the applicant presented categorical confirmed platelet values.[36] A confirmed value was based on a consecutive lab value within 7 days. If that value was in the same or worse category, the initial value was confirmed. If the consecutive value was in a better category, however, then the value was confirmed as the second value. By this algorithm, the applicant systematically chose the higher of the two platelet count values to represent the "confirmed" value. This analysis is not shown in this document.

Figure 9 presents each patient's nadir platelet count by baseline platelet count for CS6-pivotal and CS16-HTG. The empirical cumulative distribution functions for % change from baseline to nadir platelet count are shown in Figure 10 for both CS6-pivotal and CS16-HTG, allowing one to note the proportion of patients in each arm of each trial that had a % reduction in platelets of any amount of interest (or greater). For example, it can be easily discerned that ~55% of patients assigned to VLN in CS6-pivotal had ≥50% reduction in platelet count from baseline to on-study nadir.

[36] CSR CS6-pivotal, Table 65; CSR CS16-HTG, Table 52

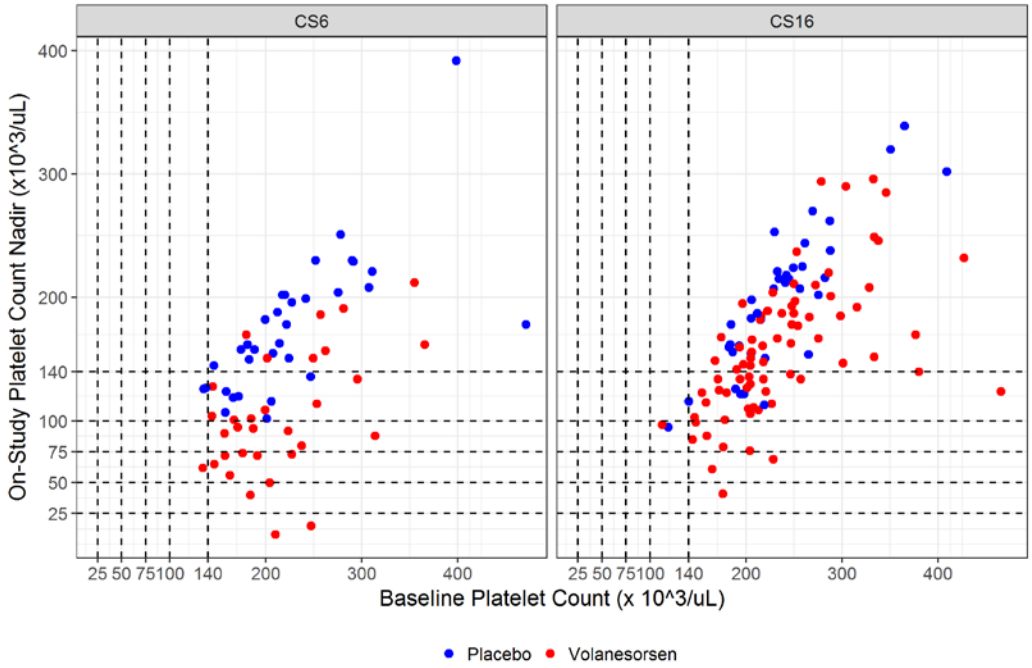


Figure 9. On-Study Platelet Count Nadir by Baseline Value
Source: *adlb.xpt* dataset from each trial

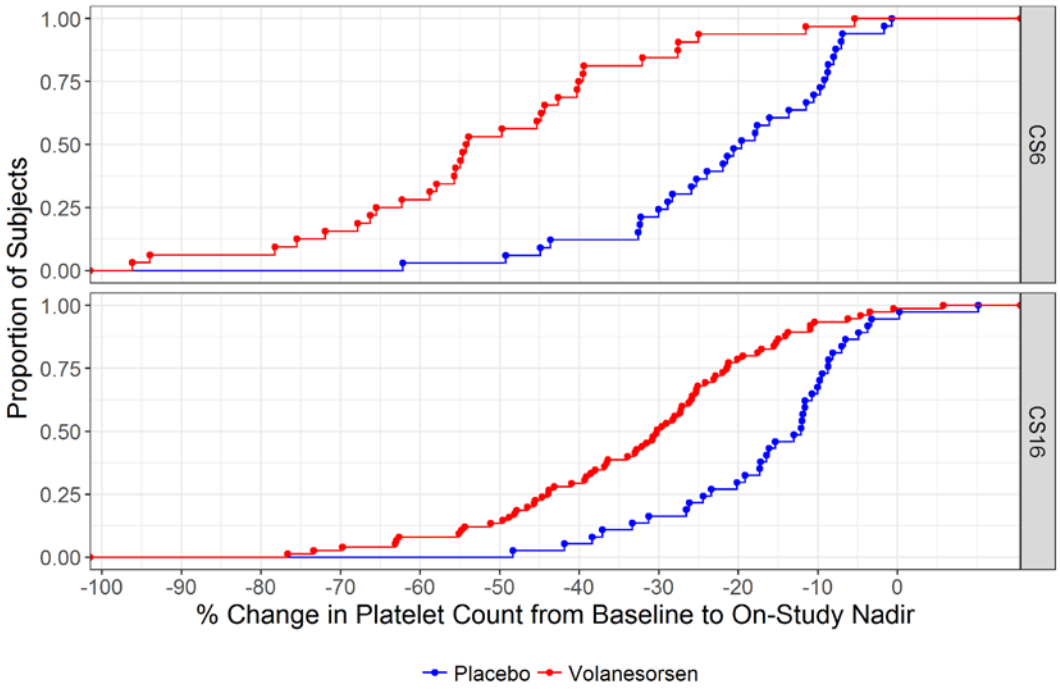


Figure 10. Empirical Cumulative Distribution Functions for % Change from Baseline to Platelet Count Nadir
Source: *adlb.xpt* dataset from each trial

Patients with Platelet Decreases to <50,000/mm^3

Using the cut-off date of August 31, 2017, from the 4-month safety update, which included patients in the ongoing CS7-OLE, 8 out of 189 (4%) VLN-exposed patients compared with none of the 100 placebo-treated patients in the Phase 2/3 program had a platelet reduction to <50,000/mm^3. Seven of the 8 are patients with FCS; i.e., 8% of patients with FCS exposed to VLN have had a platelet count <50,000/mm^3.

The incidence rate of platelet count <50,000/mm^3 is summarized by individual Phase 2 or Phase 3 controlled clinical trial in the table below. Looking at incidence rates rather than cumulative incidence proportions can be helpful, given the differing follow-up times between treatment arms (due to greater discontinuation on VLN than placebo) and between studies. In CS6-pivotal, the incidence rate was 11 patients per 100 patient-years. No patients in the placebo group experienced a platelet count <50,000/mm^3.

Table 46. Incidence rate of platelet count <50,000/mm^3 per 100 patient-years by clinical trial

	Placebo				VLN 300 mg			
Trial	Unique subjects with Platelets < 50k	Patients in trial	Patient Years[1]	Events per 100 PY	Unique subjects with Platelets < 50k	Patients in trial	Patient Years[1]	Events per 100 PY (95% CI)
CS2	0	24	11.57	0.0	1	28	12.31	8.1 (1.5, 34.7)
CS6	0	33	34.21	0.0	3	33	27.77	10.8 (3.7, 27.4)
CS16	0	38	25.61	0.0	1	75	47.92	2.1 (0.4, 10.9)
CS7								
VLN in CS6	-	-	-	-	0	14	10.74	0 (0, 26.3)
VLN in CS16	-	-	-	-	0	3	0.6	0 (0, 86.5)
Treatment naïve[2]	-	-	-	-	3	43	25.51	11.8 (4.1, 29.5)

[1]Patient years were calculated from the time of randomization to the time of the first platelet measurement < 50,000/mm^3 or to the last recorded platelet measurement for each subject, whichever occurred first.

[2]Treatment naïve patients in CS7 include 30 patients previously randomized to placebo in CS6, 2 patients randomized to placebo in CS16, and 11 patients not previously enrolled in any trial

Patient (b) (6) with a platelet nadir of 17,000/mm^3 occurring during CS7-OLE was not included in this analysis due to timing of submission after analysis completed.

Source: Dr. Andraca-Carrera

Table 47 lists the 9 patients in the clinical program with platelet nadir <50,000/mm^3 in chronologic order. The cases that triggered enhanced monitoring are shaded. Patients with nadir <25,000/mm^3 are bolded. The latest report, submitted 21 February 2018, is included in this table.

Table 47. Patients treated with VLN with platelet nadir <50,000/mm^3 in clinical development program

Study Pt ID	Preferred Term	Platelet count prior to first dose	Platelet Nadir	Time to Platelet count <50,000/mm^3	Duration	Associated Bleeding Events	Intervention/Disposition Antibodies
(b) (6)	NA	101,000	49,000	92 days	Unknown	None	Patient had finished treatment on Day 85, was in the follow-up period when nadir occurred, platelet count on Day 127 was 59,000; Day 176 was 67,000 Negative ADA No pharmacologic intervention
	Thrombocytopenia	188,000	41,000	51 days	14 days	Injection site hemorrhage	Dose pause after reached first nadir (2 doses missed) Re-challenge with weekly VLN experienced second drop in platelet below 50,000/mm^3. VLN D/C Positive for anti-plt IgG Negative for anti-plt IgM Negative for anti-PF4 IgG and IgM Negative ADA IM dose of Medrol for pneumonia
	Platelet count decreased	174,000	40,000	92 days	61 days	None	Dose Pause (8 doses missed) Re-challenge – VLN weekly dosing in OLE No steroids Negative ADA

Study Pt ID	Preferred Term	Platelet count prior to first dose	Platelet Nadir	Time to Platelet count <50,000/mm^3	Duration	Associated Bleeding Events	Intervention/Disposition Antibodies
(b) (6)	Thrombocytopenia; Platelet count decreased	253,000	**15,000**	134 days	32 days	Epistaxis, spontaneous hematoma, conjunctival hemorrhage	Hospitalization, prednisone, permanent D/C VLN **One of the cases that triggered enhanced platelet monitoring (every 2-week platelet count)** Anti-PF4 IgM positive Anti-platelet IgG negative Negative GPIIb/IIIa Negative ADA at time of event – was positive Day 341
	Thrombocytopenia	210,000	**8,000**	257 days	36 days	Epistaxis, petechiae	Hospitalization, prednisone, IVIG, permanent D/C VLN **One of the cases that triggered enhanced platelet monitoring (every 2-week platelet count)** Anti-PF4 IgM positive (baseline and post-BL) Anti-platelet IgG positive Positive GPIIb/IIIa
	Thrombocytopenia	272,000	28,000	155 days	10 days	Hematoma left arm (tourniquet site), ecchymosis right shoulder	Patient in CS6-pivotal on placebo switched to VLN in CS7-OLE. Platelet count began decline within 4 weeks of VLN treatment. Dose was paused, resumed with biweekly dosing, then discontinued due to low platelets. Prednisone x 12 days Negative ADA

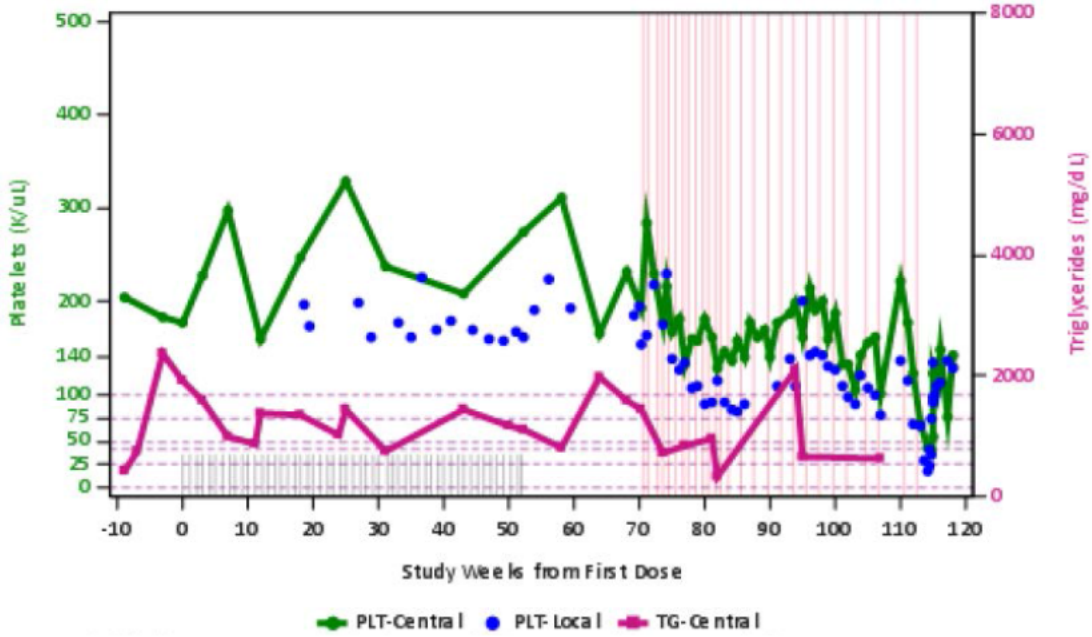
Study Pt ID	Preferred Term	Platelet count prior to first dose	Platelet Nadir	Time to Platelet count <50,000/mm^3	Duration	Associated Bleeding Events	Intervention/Disposition Antibodies
(b) (6)	Thrombocytopenia	252,000	**15,000**	80 days	57 days	None	Patient in CS6-pivotal on placebo switched to CS7-OLE Tx with Prednisone **This case triggered enhanced platelet monitoring (every week platelet count)** Positive IgG anti-plt Ab Positive IgM PF4 Ab ADA through Day 46 negative
	Low platelets x 2 Thrombocytopenia	213,000	37,000	78 days	140 days	Epistaxis	Switched to biweekly dosing, however platelet count <50,000 and prednisone started ADA negative (evaluated through Study Day 127)
	Thrombocytopenia	193,000	**17,000**	300 days	6 days	None	Switched to biweekly dosing, weekly monitoring of platelet, platelet <50,000 and prednisone started

Reviewer comment: In this reviewer's opinion, the following points are considered to be important after review of these cases:

- *Four of the cases had platelet antibody evaluations available; no consistent pattern was observed in these patients. In cases where data were available, most patients in this cohort were anti-VLN antibody negative. There is insufficient evidence to determine conclusively whether an immune-mediated etiology is responsible for VLN-induced thrombocytopenia in this group (see the hematology consultative review for further details).*
- *Although no patient had a major bleeding event, 4 of these patients had clinical bleeding (events of epistaxis, petechiae, and gingival bleeding were reported, excluding bleeding at injection site).*
- *The timing of onset to platelet count <50,000/mm^3 was highly variable, ranging from 51 to 300 days; therefore, the potential to predict when patients would be expected to experience a platelet count <50,000/mm^3 and possibly allow more flexible monitoring based on duration of treatment exposure is lacking.*
- *In cases where follow-up information was available, platelet count recovered with discontinuation of study drug with or without additional treatment (6 of the 9 patients*

received steroids, including 1 patient who required steroids and IVIG). However, it is of concern that repeated treatment of low platelet counts with steroids in patients wishing to continue treatment with VLN may lead to steroid-related morbidity.

- *In 3 cases, lengthening the VLN dosing interval did not stabilize platelet count and required VLN discontinuation.*
- *Two patients in this cohort were rechallenged with weekly VLN dosing – one patient was able to maintain platelet count above 100,000/mm^3, but the other was not and had a second platelet nadir <50,000/mm^3. There is insufficient information, at this time, to predict who is likely to tolerate a rechallenge with VLN treatment.*
- *Four patients participating in CS7-OLE had a platelet count <50,000/mm^3 under enhanced platelet monitoring, including the most recent case of a patient with platelet nadir of 17,000/mm^3 despite weekly platelet assessments. This patient's graphical profile is presented below. The patient was a 34-year-old female with FCS, no history of pancreatitis, and was treated with placebo in CS6-pivotal for 52 weeks before receiving VLN in the open-label trial, CS7-OLE.*



Short vertical gray lines represent treatment with placebo in CS6-pivotal. Long pink vertical lines represent treatment with VLN in CS7-OLE.

Figure 11. Patient Profile (b) (6)

Source: Response to FDA IR, submitted 22 March 2018

- *Despite the patient and Investigator complying with the protocol-directed platelet monitoring (at a minimum weekly) and dose adjustment, Grade 4/life-threatening thrombocytopenia occurred approximately 300 days after starting treatment with VLN. It appears that the platelet monitoring and dose adjustment may not prevent thrombocytopenia, 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*

Discontinuations due to platelet abnormalities

In CS6-pivotal, 5 VLN-treated patients discontinued due to platelet-related abnormalities. Two of these patients had platelet counts <25,000/mm^3 requiring hospitalization and were described in the table above.

In CS16-HTG, 2 VLN-treated patients discontinued due to platelet-related abnormalities. Patient (b) (6) experienced platelet counts <50,000/mm^3, was re-challenged with VLN, developed low platelet count and was discontinued (reason for discontinuation listed as "Other"). An additional CS16-HTG patient discontinued due to thrombocytopenia (Pt (b) (6)).

In CS7-OLE, using the 4-month safety update data cut-off, there were 5 patients who discontinued due to thrombocytopenia; 3 of these patients were due to platelet counts that were below 50,000/mm^3 and are included in Table 47.

Adverse Events Related to Platelet Count or Bleeding Events

- Reduced Platelet Count Event Terms

In CS6-pivotal and CS16-HTG, a higher proportion of VLN-treated compared to placebo-treated patients had adverse events reported related to a reduced platelet count. Not all cases of thrombocytopenia or platelet count reductions were reported as adverse events, and it is unclear whether investigators employed a systematic approach to determining whether a reduction in platelet count qualified as an "adverse event" and whether such an event should be reported as a decrease in platelet count or thrombocytopenia. Therefore, the number of events portrayed in the following table is lower than the actual number of cases that occurred in the study, and a distinction between the event terms should not be overinterpreted.

Table 48. Treatment-emergent adverse events related to reduced platelet count – CS6-pivotal & CS16-HTG

	CS6-pivotal		CS16-HTG	
	PBO N=33	VLN N=33	PBO N=38	VLN N=75
	n (%)	n (%)	n (%)	n (%)
Platelet count decreased	1 (3)	10 (30)	2 (5)	3 (4)
Thrombocytopenia	0	4 (12)	2 (5)	10 (13)

Source: CSR CS16-HTG, Table 14.3.1.3.1a

In the CS7-OLE 4-month safety update, "platelet count decreased" AEs were reported in 9 patients overall [7 (16%) patients in the treatment-naïve group and 2 (14%) patients in the CS6-VLN group] and "thrombocytopenia" in 6 patients overall [5 (12%) patients in treatment-naïve group and 1 (7%) in the CS6-VLN group].

- Bleeding Event Terms

Potential bleeding events were tabulated below using the MedDRA Hemorrhage Standardized MedDRA Query (SMQ). SMQs are validated sets of MedDRA terms used to investigate specific safety topics. The Hemorrhage SMQ includes preferred terms that refer not only to clinical bleeding events but also to abnormal laboratory values (e.g., decreased hemoglobin), which may or may not be caused by bleeding.

Using the Hemorrhages SMQ, a higher incidence of patients in CS6-pivotal experienced at least one event with VLN treatment - 16 (49%) patients with 45 events compared with 4 (12%) patients with 5 events with placebo. A higher incidence of bleeding events derived from the Hemorrhage SMQ was also observed with VLN treatment compared to placebo in CS16-HTG: 21 (28%) patients with 70 events in the VLN group vs. 6 (16%) patients with 7 events in the placebo group (Table 49).

In CS7-OLE, in the 4-month safety update, patients in the treatment-naïve group and patients in the CS6-VLN group had potential bleeding events on VLN treatment. A total of 20 (47%) treatment-naïve patients reported 32 events and 6 (43%) patients in the CS6-VLN group reported 13 events. Bleeding at the injection site was observed, but also ecchymosis, epistaxis, hematuria, hemorrhagic cystitis, conjunctival hemorrhage, gingival bleeding, genital hemorrhage, contusion, and hematoma.

Table 49. Treatment Emergent Adverse Events Hemorrhage SMQ – CS6-pivotal & CS16-HTG (Applicant Analysis)

	CS6-pivotal				CS16-HTG			
	PBO N=33	VLN N=33	PBO	VLN	PBO N=38	VLN N=75	PBO	VLN
	n (%)	n (%)	*Events*	*Events*	n (%)	n (%)	*Events*	*Events*
Hemorrhage SMQ TEAE	**4 (12)**	**16 (49)**	***5***	***45***	**6 (16)**	**21 (28)**	***7***	***70***
Injection site bruising	0	5 (15)	*0*	*15*	1 (3)	11 (15)	*2*	*37*
Epistaxis	0	5 (15)	*0*	*7*	0	1 (1)	*0*	*1*
Petechiae	0	4 (12)	*0*	*4*	0	1 (1)	*0*	*1*
Injection site hematoma	0	2 (6)	*0*	*4*	1 (3)	2 (3)	*1*	*3*
Vaginal hemorrhage	0	2 (6)	*0*	*2*	0	0	*0*	*0*
Conjunctival hemorrhage	0	1 (3)	*0*	*1*	0	0	*0*	*0*
Contusion	1 (3)	1 (3)	*1*	*1*	1 (3)	3 (4)	*1*	*5*
Gingival bleeding	0	1 (3)	*0*	*1*	0	0	*0*	*0*
Hematocrit decreased	1 (3)	1 (3)	*1*	*1*	0	0	*0*	*0*
Hematoma	0	1 (3)	*0*	*2*	1 (3)	0	*1*	*0*
Hemoglobin decreased	2 (6)	1 (3)	*2*	*1*	0	2 (3)	*0*	*2*
Hemorrhage	0	1 (3)	*0*	*1*	0	2 (3)	*0*	*3*
Immune thrombocytopenia purpura	0	1 (3)	*0*	*1*	0	0	*0*	*0*
Injection site hemorrhage	0	1 (3)	*0*	*1*	0	7 (9)	*0*	*10*
Mouth hemorrhage	0	1 (3)	*0*	*1*	0	0	*0*	*0*

	CS6-pivotal				CS16-HTG			
	PBO N=33	VLN N=33	PBO	VLN	PBO N=38	VLN N=75	PBO	VLN
	n (%)	n (%)	*Events*	*Events*	n (%)	n (%)	*Events*	*Events*
Rectal hemorrhage	0	1 (3)	*0*	*1*	0	0	*0*	*0*
Spontaneous hematoma	0	1 (3)	*0*	*1*	0	0	*0*	*0*
Hemoptysis	1 (3)	0	*1*	*0*	0	0	*0*	*0*
Ecchymosis	0	0	*0*	*0*	0	2 (3)	*0*	*3*
Hematuria	0	0	*0*	*0*	0	2 (3)	*0*	*2*
Bleeding time prolonged	0	0	*0*	*0*	0	2 (3)	*0*	*3*
Eye hemorrhage	0	0	*0*	*0*	0	1 (1)	*0*	*1*
Occult blood positive	0	0	*0*	*0*	0	1 (1)	*0*	*1*
Hematochezia	0	0	*0*	*0*	1 (3)	0	*1*	*0*
Hematoma infection	0	0	*0*	*0*	1 (3)	0	*1*	*0*

Source: CSR CS6-pivotal Addendum 1 Table 14.3.2.14; CSR CS16-HTG Addendum 1 Table 14.3.3.5adhoc1
On-study all bleeding TEAE occurred after the first dose of the study drug through the end of the study

In CS6-pivotal and CS16-HTG, most of the bleeding events occurred at the injection site. In an FDA-analysis of CS6-pivotal, after excluding bleeding events at the injection site and terms that only related to a laboratory value (e.g., decreased hemoglobin), there was still a higher proportion of VLN-treated patients with clinical bleeding compared to placebo (36% versus 6%), with the most frequent bleeding events being epistaxis and petechiae (Table 50). In CS7-OLE, bleeding at the injection site accounted for 7 of the 32 events in treatment-naïve patients and 7 of the 13 events in the CS6-VLN group. Excluding bleeding at the injection site, epistaxis (n=5 events in 4 patients) was the most often reported bleeding event in the treatment-naïve group.

Table 50. Clinical bleeding excluding bleeding at injection site and lab-related values – CS6-pivotal

	Placebo (N=33)	VLN (N=33)	Placebo	VLN
	Patients, n (%)	*Patients, n (%)*	*# Events*	*# Events*
Hemorrhage SMQ	4 (12%)	16 (49%)	5	45
Hemorrhage SMQ, excluding injection site-related events & lab-related events	2 (6%)	12 (36%)	2	23
Epistaxis	0	5 (15%)	0	7
Petechiae	0	4 (12%)	0	4

Source: Clinical Reviewer table from CS6 *adae* dataset

Anti-platelet/Anti-coagulant Medications and Bleeding Events

Overall, 13 (20%) of patients in CS6-pivotal reported concomitant use of medications affecting coagulation or platelet function. The most common agent used was aspirin and its salts. One patient in each treatment group reported clopidogrel as a concomitant medication.

An FDA analysis of bleeding events with or without concomitant anti-coagulant or anti-platelet medication focused on patients reporting clinical bleeding events and excluded patients without clinical bleeding (e.g. abnormal laboratory value or diagnostic terms such as immune thrombocytopenic purpura). Patients who were taking these concomitant drugs were more likely to experience bleeding in both VLN (63%) and placebo (20%) than patients who were not taking them (28% on VLN and 4% on placebo). An analysis for an interaction between VLN and anti-platelet/anti-coagulants with respect to bleeding events was non-significant, but the small number of events preclude definitive conclusions.

One limitation of this analysis is that anti-coagulant/anti-platelet use includes both baseline and concomitant (post-randomization) use. Because this is a post-randomization characteristic, one cannot guarantee that patients who used anti-coagulants/anti-platelet were similar in both treatment groups.

Table 51. Bleeding Events by Use of Anti-coagulant and/or Anti-platelet Medications – CS6-pivotal

		Volanesorsen			Placebo		
		Total	Concomitant anti-plt/anti-coag		Total	Concomitant anti-plt/anti-coag	
			Yes	No		Yes	No
Bleeding	Yes	**12**	5	7	**2**	1	1
	No	**21**	3	18	**31**	4	27
		36%	63%	28%	6%	20%	4%

Dr. Andraca-Carrera. The last row denotes the percentage of patients in each column who had a bleeding event.

Reviewer Comment: The small number of patients on anti-platelet/anti-coagulant medications, and relatively small number of patients with clinical bleeding events, limits a definitive conclusion regarding how these medications may affect bleeding in a VLN-treated patient.

Platelet Count and Bleeding Events

The plot below summarizes clinical bleeding events (excludes bleeding at injection site or lab-related event terms) in CS6-pivotal by platelet count. Among patients with multiple bleeding events, the bleeding event with the lowest prior platelet measurement was selected. If multiple events had the same prior platelet measurement, then the first bleeding event was selected.

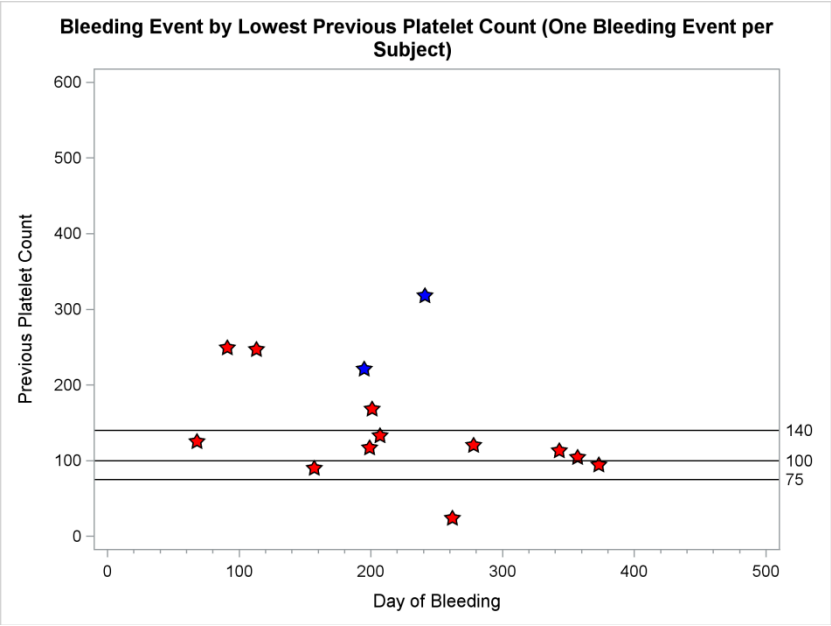


Figure 12. Bleeding event by lowest previous platelet count – CS6-pivotal
Red – VLN group, Blue – placebo group
Source: Dr. Andraca-Carrera

Reviewer Comment: There does not appear to be a correlation between platelet count and risk of bleeding. However, it is concerning that clinical bleeding occurred for most patients above 75,000/mm^3, 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 VLN has not been conducted.

Platelet Count by Baseline Body Weight

The applicant has conducted analyses of the effect of body weight on platelet count and is proposing adjustment of VLN dosing frequency by baseline body weight based on their interpretation of the data. A statistical association between platelet count percent decrease and body weight was observed, suggesting that patients with lower weight may have an increased risk of platelet reduction (Figure 13). The trend observed may be more representative of a relationship between body weight and gradual platelet reductions, however, since not all of the patients who exhibited large reductions in platelet count had body weight <70kg. The clinical pharmacology review team has reviewed their proposal and justification to support the new dosing regimen. The reader is referred to the clinical pharmacology review for further discussion.

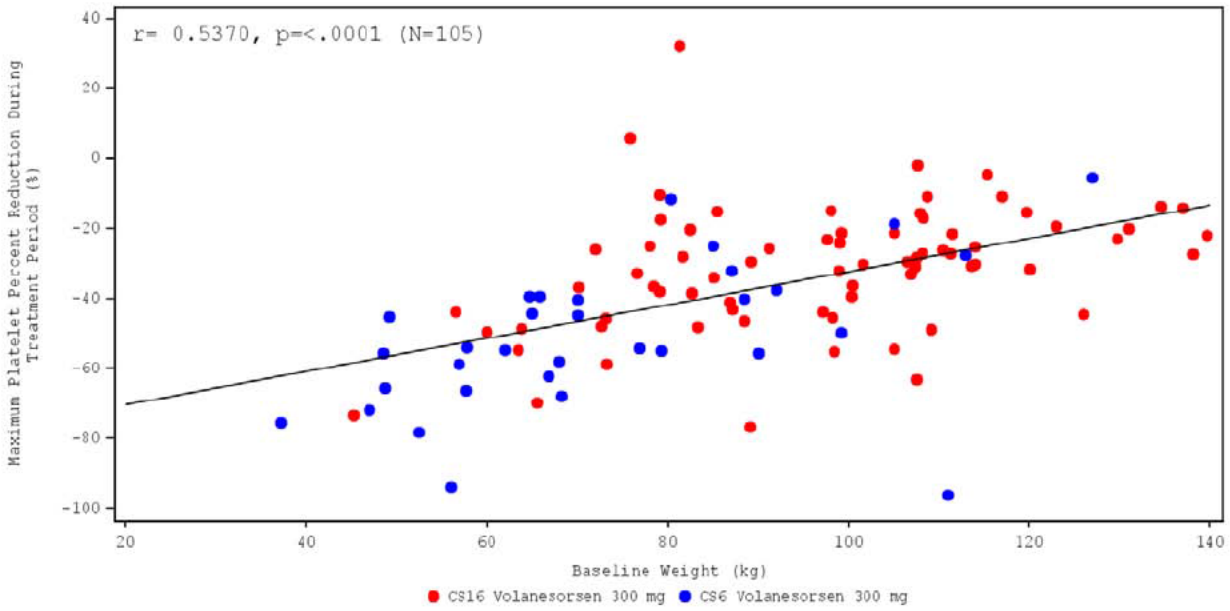


Figure 13. Correlation Between Maximum Percent Reduction in Platelets During the On-Treatment Period Versus Baseline Weight (Studies CS6-pivotal and CS16-HTG, N = 105)

Note: Baseline platelet count was defined as the average of all pre-dose results including local labs and unscheduled visits. Baseline weight was defined as the last assessment prior to the first dose of study drug. The on-treatment period was defined as the period from the first dose date through the last dose date + 28 days.

Source: ISS, Figure 12

Investigation into Mechanism of VLN Effect on Platelets

The applicant conducted investigations to evaluate the potential mechanism for VLN-associated thrombocytopenia which encompassed evaluations for decreased platelet production, platelet sequestration, or increased consumption. These investigations have been reviewed by an FDA hematologist who has concluded that the mechanism studies are insufficient to provide a definitive explanation for VLN-induced thrombocytopenia due to study deficiencies, such as the limited number of samples tested, baseline imbalances, lack of real-time sampling, and limited or no human samples tested. The reader is referred to hematology consultative review for further details.

Table 52. Summary of the applicant investigation into mechanism of thrombocytopenia observed with VLN treatment

Study (trial ID)	The Applicant's Results			Reviewer Assessments
Antibody investigations				
Drug independent antiplatelet antibodies[1]	Arm	Baseline	Treated	Imbalance noted at baseline. Treatment emergent positivity doubled in both cohorts.
	VLN (24)	12.5%	25%	
	Placebo (17)	5.9%	11.8%	
Drug dependent antiplatelet antibodies	Negative in 24 patients on VLN and 17 patients on placebo			Tested in 22% (41/190) of patients exposed to volanesorsen[2].

Study (trial ID)	The Applicant's Results	Reviewer Assessments
IgG anti-PF4 antibodies	Negative in 24 patients on VLN and 17 patients on placebo	Tested in 22% (41/190) of patients exposed to volanesorsen[2].
IgM anti-PF4 antibodies[1]	Positive in 4 patients on VLN (3 with grade 4 thrombocytopenia) and 1 on placebo.	Inconclusive results.
Anti-volanesorsen and other drug antibodies (ADA)	90% of subject received VLN in CS6 trial tested positive for ADA. No known association between ADA and thrombocytopenia	Clinical pharmacology review found no consistent effect of ADA status on platelet reduction.
Other investigations		
Cytokine levels at baseline	A panel of 66 cytokines were measured in all CS6 trial patients. Increased IL-23, MIP-1beta and SDF1, and decreased TWEAK at baseline levels correlated with lower platelet counts.	No cytokine levels measured at the time of thrombocytopenia. Patients studies had dissimilar baseline cytokine levels between the VLN and placebo groups.
Platelet aggregation tests (Study AS19[3])	13-week study in Cynomolgus monkeys (14 males and 14 females), no platelet abnormality reported. Platelet aggregation test was normal.	Platelet aggregation in FCS patients on VLN is unknown.
Platelet activation by volanesorsen (IS09)	Platelet activation markers were unchanged after exposed to volanesorsen. The platelet activation increased in presence of chylomicrons.	No baseline or at the time of thrombocytopenia testing in patients.
Platelet pooling	In CS6, baseline spleen volume was 508 cc in VLN group and 454 cc in placebo group. At week 52, mean change of +107 cc in VLN group and +32 cc in placebo group.	Mild increase in spleen volume (~100cc) is unlikely to be clinically significant.
Platelet Consumption by coagulopathy	No evidence of TMA, DIC, TTP, or HIT.	Limited number of patients were evaluated except for PTT, PT, INR.
Thrombotic or embolic events	No evidence.	Limited safety data base
Megakaryocyte inhibition (Studies AS02[3] and AS11)	Study AS02 was a 13-weeks study in Cynomolgus monkeys (38 males and 38 females), no decrease of platelets was found. bone marrow samples examined and no abnormality reported. Study AS11 was a 39-week study in Cynomolgus monkeys (48 males and 48 females). Thrombocytopenia and bleeding events were seen in 5 monkeys. Platelet activation test results showed no change. No coagulation abnormality was found. No megakaryocyte inhibition was concluded based on two animal studies.	The thrombocytopenia events were seen in Monkeys after 39-weeks exposure to volanesorsen but not in those after 13-weeks. In CS6, there were limited number of patients who had bone marrow evaluation. Of the 2 patients with bone marrow evaluation, results were reported to be normal.

TMA = thrombotic microangiopathy, DIC = disseminated intravascular coagulation, TTP= thrombotic thrombocytopenic purpura, HIT = a classical heparin-induced thrombocytopenia-like mechanism, VLN = volanesorsen.

1. Four patients were positive for both anti-PF4 IgM and drug-independent anti-platelet GPIIb/IIa. Their platelet nadirs were, 8, 15, 50 and 88 x 10^9/L.
2. Of the 41 patients selected for antibodies investigation, 70% (29/41) of them has a diagnosis of FCS.
3. Exposure duration of 13 weeks in studies AS02 and AS19 were 1/3 of AS11 study treatment duration. The exposure duration of AS02 and AS11 may be insufficient to affect platelets.

Source: Adapted from Hematology consult review

Other Hematologic Parameters

Review of the provided shift tables for hemoglobin did not demonstrate a meaningful difference between treatment groups in Study CS6-pivotal. The average change in hemoglobin in VLN-treated patients in study CS6-pivotal at Week 52 was -0.3 g/dL; changes from baseline were generally small over time. There were also no imbalances observed for preferred terms related to hemoglobin (e.g. anemia, hematocrit decreased, hemoglobin decreased) in Study CS6-pivotal.

A higher percentage of patients treated with VLN in Study CS6-pivotal exhibited a shift to a lower category in white blood cell count. Twelve (43%) VLN-treated patients shifted from a WBC category of >3,500/mm^3 to a 2,500-3,500/mm^3 category (Grade 1 mild) versus 1 (3%) of placebo-treated patients in study CS6-pivotal. One VLN-treated patient exhibited a change from the >3,500/mm^3 category to 1,500 to 2,499/mm^3 category. No patients had a WBC <1,500/mm^3 (Grade 3 severe). The significance of these small changes/shifts in white blood cell count are unclear. Similar shifts in VLN-treated patients were not observed in study CS16-HTG.

6.5.2. Injection Site Reactions

In the original NDA submission, the applicant only considered a local cutaneous reaction at the injection site (LCRIS) to be an event that started on the day of the injection, persisted for at least 2 days, and was reported using one of the following descriptors regarding the injection site: erythema, swelling, pruritus, pain, or tenderness.

On review of the adverse event listings, however, it was noted that many adverse events (287 additional events) at the injection site were not captured using this definition of a LCRIS, such as injection site discoloration and injection site induration.[37] The applicant was asked to revise the definition of LCRIS to include all treatment-emergent adverse events occurring at the injection site and persisting for 2 days. The table below provides the results of this analysis.

In Study CS6-pivotal, under this revised LCRIS definition, no placebo patients reported LCRIS events and 26 (79%) of 33 VLN treated patients reported a total of 497 individual LCRIS events. The average number of injections before the first reported LCRIS was 6, with a range of 1 to 34 injections. Median (Q1, Q3) time to resolution of these events was 8 (4, 29) days.

In Study CS7-OLE, 4-month safety update, 31 (72%) of the 43 treatment-naïve patients reported 335 treatment-emergent adverse events using the revised LCRIS definition.

In Study CS16-HTG, 3 (8%) of 38 placebo patients reported 8 LCRIS events and 65 (87%) of 75 VLN-treated patients reported 1055 individual LCRIS TEAE events. Injection site reaction terms

[37] Using the original LCRIS definition, no placebo patients and 20 (61%) VLN-treated patients experienced 210 events.

reported in ≥ 15% of VLN-treated patients were erythema, swelling, pruritus, discoloration, and induration. The average number of injections before the first reported LCRIS event was 3 (range 1 to 14 injections) in the VLN-treated group.

Given that patients were not prospectively asked about injection site events either after each injection or at study visits, it is entirely possible that these numbers are underestimates of the true number of events. With weekly injections, reporting fatigue could be expected without a prospective plan to record such information. For these reasons, the applicant's descriptions of the proportion of injections accompanied by an injection site reaction (i.e., # reported events / # total injections administered) are likely unreliable and are not presented in this review.

Table 53: Treatment-emergent Local Cutaneous Reactions at the Injection Site (revised) – CS-pivotal

	Placebo N=33	VLN N=33	Placebo	VLN
	n (%)	n (%)	*Events*	*Events*
Patients reporting at least 1 LCRIS	**0**	**26 (79)**	**0**	**497**
Injection site (IS) erythema	0	22 (67)	0	197
IS pain	0	8 (24)	0	36
IS discoloration	0	7 (21)	0	22
IS induration	0	7 (21)	0	36
IS pruritus	0	6 (18)	0	47
IS bruising	0	5 (15)	0	15
IS swelling	0	4 (12)	0	18
IS hypoesthesia	0	3 (9)	0	3
IS hematoma	0	1 (3)	0	3
IS pallor	0	3 (9)	0	19
IS reaction	0	3 (9)	0	12
IS edema	0	3 (9)	0	12
IS urticaria	0	2 (6)	0	50
IS warmth	0	2 (6)	0	8
IS dryness	0	2 (6)	0	13
IS vesicles	0	1 (3)	0	1
IS scab	0	1 (3)	0	1
IS mass	0	1 (3)	0	1
IS inflammation	0	1 (3)	0	1
IS hyperesthesia	0	1 (3)	0	1
IS discomfort	0	1 (3)	0	1

Source: Response to IR; submitted 15 December 2017, Table 14.3.2.8a adhoc1

In Study CS6-pivotal, CS7-OLE, and CS16-HTG, skin discoloration at the injection site was noted in 20 to 30% of patients. Many of these events involving skin discoloration were not reported to resolve: In CS6-pivotal, 5 patients had 6 discoloration events that had not resolved; in CS16-HTG, 16 patients had 48 discoloration events that had not resolved; and in CS7-OLE, 8 patients had 53 discoloration events that had not resolved at the time of data cut-off for the 4-month safety update.

In studies CS6-pivotal and CS16-HTG, 10 patients discontinued treatment due to a LCRIS event using this revised definition; 1 patient in Study CS6-pivotal (b) (6) and 9 patients in Study CS16-HTG. As of the 4-month safety update for CS7-OLE, no patients had discontinued due to LCRIS.

The patient in study CS6-pivotal discontinued treatment with VLN due to reactions at the injection site, prostration, and fatigue. A narrative of this patient follows.

- Patient (b) (6) – a 51-year-old white female with FCS was randomized to VLN 300 mg/weekly and received a total of 13 doses. She reported AEs at the injection site on Study Day 1. In total, she experienced 18 "mild" AEs and 7 "moderate" AEs at the injection site. The mild AEs resolved within 3 to 8 days of onset. She also experienced 7 moderate AEs of erythema, edema, pain, burning, hyperpigmentation, loss of sensitivity and depression in cutaneous surface of the injection site. Of these 7 AEs, 4 resolved (75 days in duration) and 3 were ongoing at the end of the follow-up period. No concomitant medications were administered for these IS reactions. The patient discontinued from VLN treatment after 13 weeks of treatment due to IS reactions, prostration, and fatigue, but continued in the study and completed follow-up on 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 VLN.

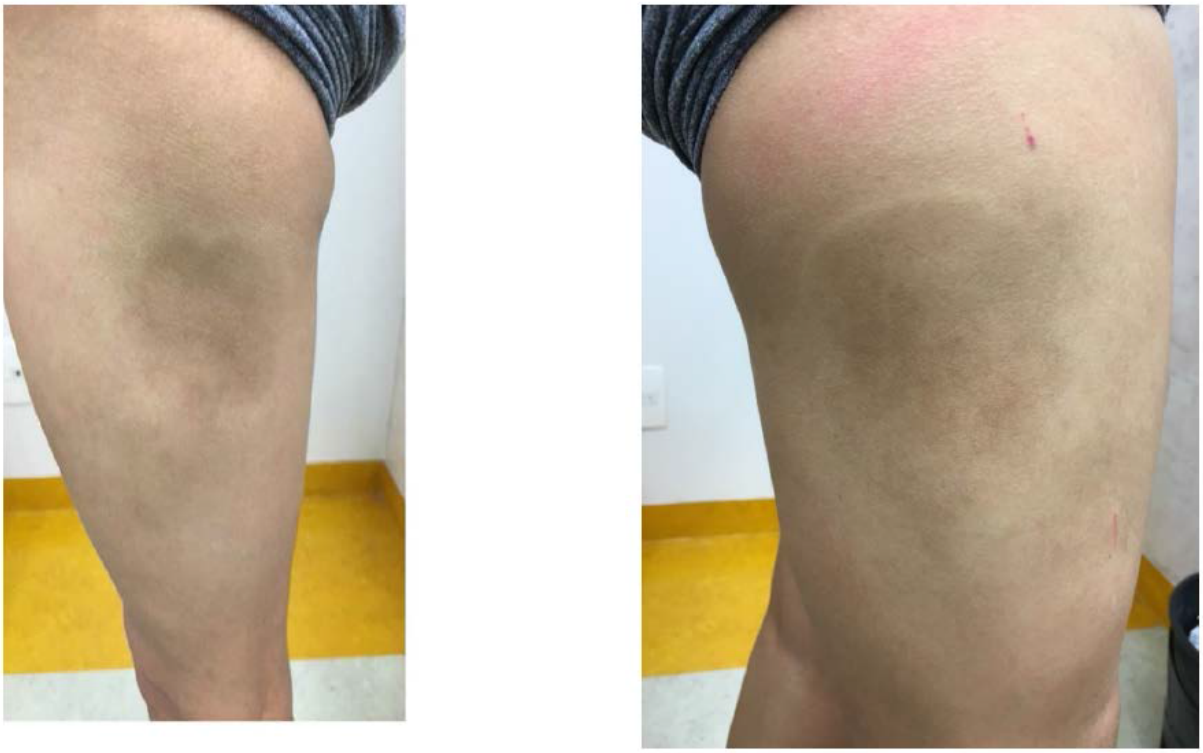


Figure 14: (b) (6) – Injection site reaction 4 months following last dose of VLN
Source: Response to IR submitted 15 December 2017

Reviewer Comment: Despite a high incidence of LCRIS in CS6-pivotal, only 1 patient is reported to have discontinued study treatment due to injection site reactions. The hyperpigmentation observed at injection sites treated with VLN may be due to post-inflammatory hyperpigmentation. There were no other reports in CS6-pivotal or CS16-HTG of skin depression at the injection sites.

6.5.3. Flu-like reactions

The applicant defined flu-like reactions (FLR) as either (a) "influenza-like illness" or (b) 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 injection. Case report forms did not prospectively ask about each of these symptoms; therefore, a patient and investigator would have had to report up to 3 signs/symptoms as "adverse events" within a narrow time window to meet the definition for FLR under (b), above. Thus, this approach to identifying FLR programmatically is likely insensitive since it does not appear that patients were specifically instructed to report these signs/symptoms after each dose, if they occurred.

In study CS6-pivotal, two (6%) VLN-treated patients qualified for a FLR by reporting an "influenza-like illness" within the required time frame. The severity of both events was graded

as mild and both events resolved. No action was taken with the VLN dose. No patients met the second definition of a FLR.

If the definition of FLR is broadened to include reporting of *at least one* of the related symptoms (fever, feeling of warmth, chills, myalgia, or arthralgia), an additional 7 (21%) VLN-treated patients compared with 1 (3%) placebo-treated patient in CS6-pivotal may have experienced a FLR. One of the VLN-treated patients, Patient (b) (6), withdrew from the study for the adverse events of sweating and chills associated with VLN administration; the applicant did not consider this a FLR.

- Patient (b) (6) – 58-year-old white male with FCS randomized to VLN 300 mg weekly. After receiving 27 doses, the frequency of VLN dosing was changed to biweekly due to injection site induration. After receiving his 31st dose of VLN, the patient had mild chills and sweating which resolved on the same day; mild chills, sweating and moderate muscle spasms occurred after 2 subsequent doses. The patient permanently discontinued study drug due to the event of chills and sweating with the last dose administered on Study Day 274. He received a total of 33 doses of study drug prior to discontinuation. The patient continued study with follow-up visits and assessments until completion on Study Day 413.

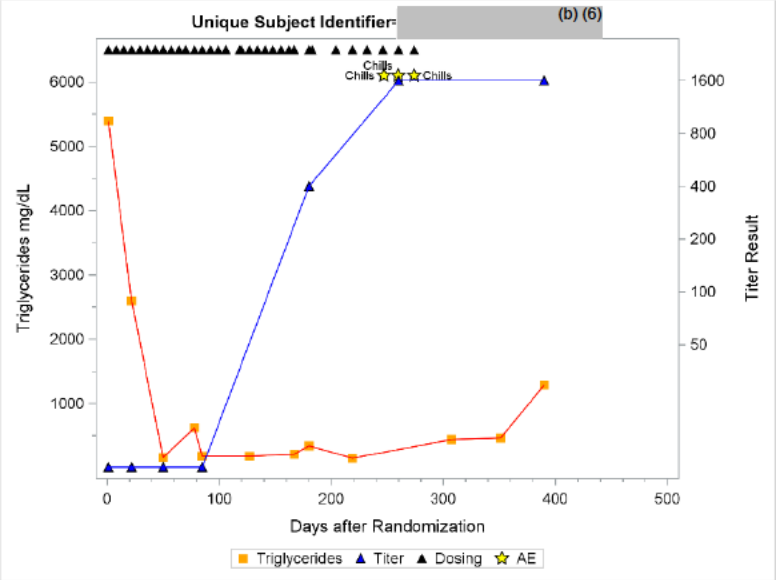


Figure 15. (b) (6) Patient Profile

Source: Dr. Andraca-Carrera

Reviewer Comment: This patient seroconverted with high-titer anti-VLN antibodies present at the time of complaints of chills and muscle pain.

As of the 4-month safety update for CS7-OLE, there were 2 patients (both in the CS6-VLN group) that met the definition for a FLR. One of these patients ((b) (6)) was hospitalized for her symptoms and had developed anti-VLN antibodies at the time of her symptoms. A brief narrative of this patient follows.

- [redacted] (b) (6), a 72-year-old female, diagnosed with FCS 36 years prior to the study start, with a history of pancreatitis and anemia, was randomized to VLN 300 mg/week in CS6-pivotal. She received 41 doses of VLN in CS6-pivotal before the dose of VLN was held due to a low platelet count of 50,000/mm^3 on Study Day 290. The patient did not restart VLN for the rest of CS6-pivotal (approximately 90-day dosing holiday) and then enrolled in CS7-OLE and received VLN 300 mg every other week. Her anti-drug antibody response was negative through Study Day 85 and converted to positive on Study Day 176 in CS6-pivotal. After being treated in CS7-OLE for approximately 6 months and receiving an additional 14 doses, the patient complained of chills, headache, fatigue, and dyspepsia, which started on the same day as dosing and lasted 3 days. The patient continued to experience this constellation of symptoms with 4 subsequent administrations of VLN and dosing was paused (1 dose). She resumed dosing and experienced moderate chills and fever that day. The following day she was admitted to the hospital for difficulty walking and myalgia. The patient was afebrile, CK was normal, and x-rays of the chest, legs, and hip were unremarkable. The patient's myalgia resolved and she was discharged from the hospital 2 days after admission. The patient discontinued the study drug due to the events of myalgia and chills. She received 41 doses of VLN in CS6-pivotal and 19 doses of VLN in CS7-OLE.

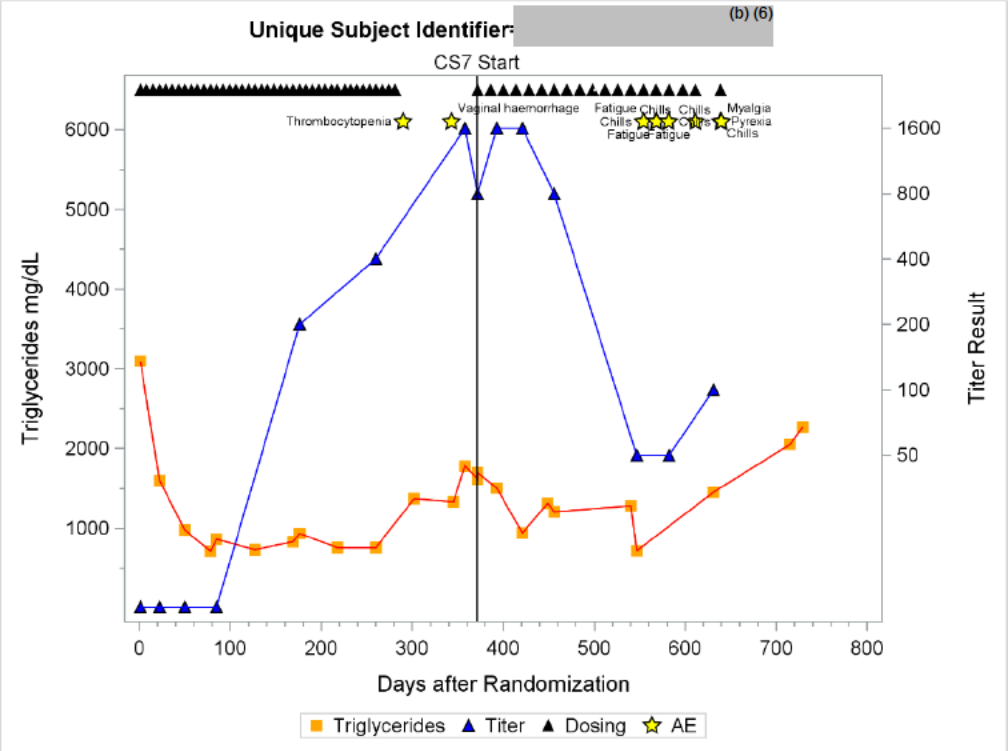


Figure 16. [redacted] (b) (6) Patient Profile

Source: Dr. Andraca-Carrera

Reviewer Comment: This case is interesting in that the patient did not exhibit these symptoms during participation in the pivotal trial, but the flu-like symptoms triggering hospitalization

occurred after repeated dosing. It is unknown if the appearance of anti-VLN antibodies occurring first on Study Day 176 of CS6-pivotal contributed to these symptoms.

In CS16-HTG, two (3%) VLN-treated and no placebo-treated patients met the definition for a FLR. No action was taken with the VLN dose; the events were mild and resolved.

Inflammation biomarkers

hsCRP was measured at the beginning of Weeks 1 (i.e., study day 1), 13, 26, and 52/Early Termination in CS6-pivotal and at Weeks 1, 13, 26/Early Termination, and 39 in CS16-HTG. A modestly higher proportion of VLN-treated versus placebo-treated patients showed a shift from a normal hsCRP to above the upper limit of normal (3 mg/L) in both CS6-pivotal and CS16-HTG. In CS6-pivotal, 11 (33%) of 33 patients in the volanesorsen group had a shift from normal to abnormal during the on-study periods compared with 9 (27%) of 33 patients in the placebo group. Three patients in each group had a peak hsCRP value >10 mg/L.

In CS16-HTG, 7 VLN-treated versus no placebo-treated patients had a shift from normal to >10 mg/L. The most marked abnormality was a shift in CRP from 2.8 mg/L (Day 1) to 346 mg/L (Day 169), when the patient experienced a systemic inflammatory response, was diagnosed as having serum sickness, and was discontinued from treatment.

6.5.1. Immunogenicity/Hypersensitivity

- Immunogenicity

Anti-drug antibodies (ADA) were analyzed at the beginning of Weeks 1, 4, 8, 13, 26, 38, 52/Early Termination, 58, and 65 in CS6-pivotal and with the same schedule up to Week 39 in CS16-HTG. Patients were given 'positive' immunogenicity (IM) status if they had at least one confirmed positive sample at any time during the treatment or post-treatment evaluation periods. Study patients were given 'negative' IM status if all evaluated IM sample results during the treatment and post-treatment evaluation periods were negative and they had at least one evaluable IM result post-dose. Otherwise, study patients were given 'unknown' IM status.

CS6-pivotal
One placebo-treated patient tested positive for ADA at baseline with a low titer of 50 through Week 8.

Of the 33 VLN-treated patients, 11 (33%) patients tested positive for ADA. The median time of onset was approximately 6 months, and the median peak titer was 400. Except for one VLN-treated patient, positivity was persistent from onset through the last evaluation. The most commonly reported TEAEs for VLN in both antibody-positive and antibody-negative patients were events related to local tolerability. Visual inspection of internally generated figures of ADA titer, TG level, and platelet count over time for the 11 patients positive for ADA did not suggest

that ADA affect either platelet count or TG levels.

CS16-HTG

Of the 75 volanesorsen-treated patients, 12 (16%) patients tested positive for ADA. The median time of onset was day 165, and the median peak titer was 600. IM response was sustained from onset through the last evaluation in all ADA-positive patients. The emergence of ADA did not appear to impact platelet count or TG level.

CS7-OLE

In the treatment-naïve group in CS7-OLE, 2 of 43 patients became positive for ADA.

Reviewer comment: Although the appearance of ADA did not appear to impact platelets or TG, the appearance of ADA, in this reviewer's opinion, may be related to adverse events in 4 cases: (1) a case of chills and sweating leading to discontinuation ((b) (6)), (2) a flu-like reaction with hospitalization ((b) (6) – narratives in previous section); (3) a serious case of serum sickness with emergence of high ADA titers ((b) (6) – narrative below); and (4) a case of anaphylaxis requiring emergent treatment ((b) (6) in a non-FCS patient with development of flu-like symptoms and anaphylaxis occurring approximately 6 weeks after patient developed anti-VLN antibodies. Narrative of the patient with serum sickness and anaphylaxis follows.

- Patient (b) (6), a 47-year-old male with hypertriglyceridemia, not taking lipid-lowering medication, randomized to 300 mg VLN weekly, was diagnosed with serum sickness. On Study Day 130 (previous VLN dose on Study Day 129), the patient experienced flu-like symptoms that resolved within 2 days with ibuprofen treatment. VLN was administered on Study Day 134, followed again by flu-like symptoms. VLN was held. The patient persisted with symptoms of groin pain, low-grade temperature prompting an unscheduled clinic visit on Study Day 146. Flu-like symptoms (muscle aches, fever) persisted and the patient was seen again for an unscheduled visit on Study Day 149. This visit was significant for the patient being febrile 102F, having elevated ALT and AST (at 3x ULN), bilirubin normal and unremarkable chest x-ray. On Study Day 153, 19 days after last dose of Study Drug, the patient reported fever of 104°F and pain. On Study Day 155, the patient had a positive anti-volanesorsen antibody test with a titer of 6400, which increased to a peak of 25,600 on Study Day 176, on Study Day 267, the result was positive with a titer of 12,800. On Study Day 157, he was started on high dose prednisone taper regimen which was stopped on Study Day 171. On Study Day 175, the rheumatologist diagnosed the patient with serum sickness. On Study Day 185, blood cultures remained negative and liver enzymes normalized (ALT 54 U/L and AST 35 U/L). The SAE of serum sickness was considered resolved. The patient permanently discontinued Study Drug; last dose on Study Day 134. This patient continued in the clinical trial off study drug.

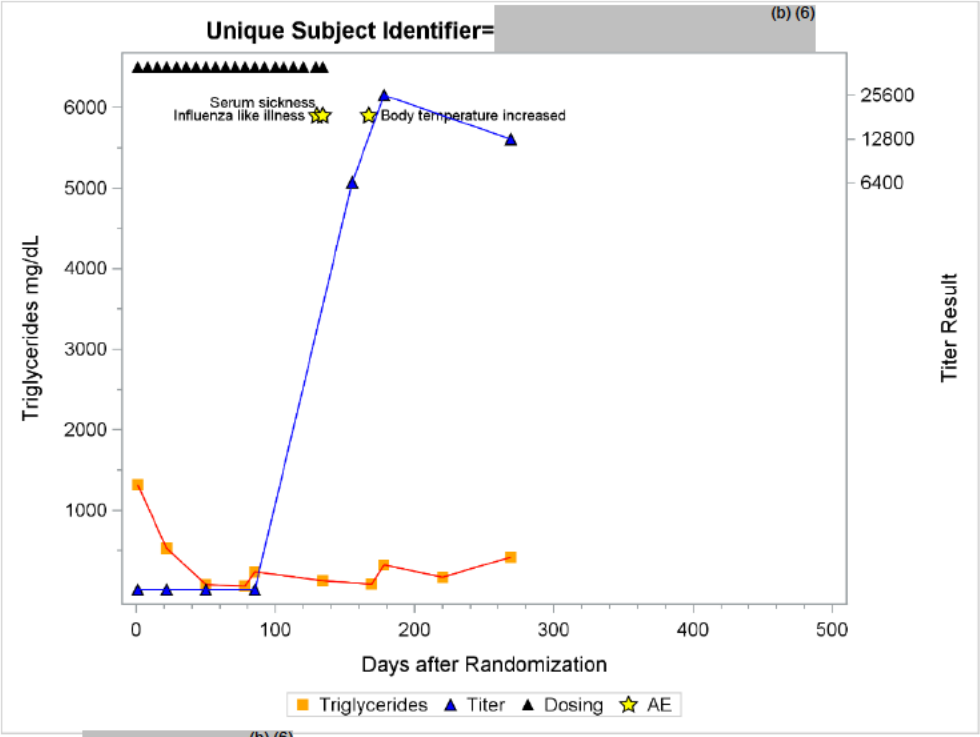


Figure 17. (b) (6) Patient Profile

Source: Dr. Andraca-Carrera

- Patient (b) (6),[38] a 40-year-old man with familial partial lipodystrophy had completed a 52-week double-blind portion of the study on placebo and was being treated with VLN in an OLE phase. On Study Day 486 (approximately 4 months after starting VLN in the open-label phase of study), the patient had flu-like symptoms (nausea/vomiting, muscle aches) within 12 hours of dosing, which persisted despite taking ibuprofen before and after VLN injections. The patient was on a dose pause (received 3 injections over 3 months) due to these symptoms (dates of injections not reported), but because he was going on vacation and over concern for pancreatitis he was administered 300 mg of volanesorsen on Study Day 593. Within 5 minutes of receiving the drug he had shortness of breath, nausea, diaphoresis, and "profound somnolence". He was taken to the ER via ambulance and was hypotensive, tachycardic, and tachypneic. He was assessed as having an anaphylactic reaction and given epinephrine, Solu-Medrol, Benadryl and IV fluids. EKG showed sinus tachycardia, echocardiogram was within normal limits, and chest xray was unremarkable. He was admitted to the hospital, treated, and later discharged on prednisone; study drug was discontinued. Work-up by allergist could not determine if the event was IgE-mediated due to lack of response to control in skin-prick testing. The allergist noted that although the patient did not have pruritus, hives, or rash typical of an IgE-mediated reaction, the

[38] Study CS17, which is investigating the use of VLN among certain patients with familial partial lipodystrophy, was not submitted to the NDA. This case, however, was included in the 4-month safety update since it was a serious unexpected suspected adverse reaction.

hypotension could have prevented these events from occurring. This patient was anti-VLN antibody negative until Study Day 449, flu-like symptoms began to occur with dosing around Study Day 486; the patient was positive for anti-VLN antibodies (titer 200) at the next ADA evaluation on Study Day 540, at an unscheduled visit (titer 800), and on Study Day 624 (titer 800). No further testing results of ADA provided.

- Hypersensitivity

A higher proportion of VLN-treated patients compared to placebo-treated patients reported an adverse event within the Hypersensitivity SMQ (Table 54). Erythema and pruritus were reported by the largest number of patients. Injection site urticaria had the highest number of events (n=64) in 2 patients treated with VLN.

A similar pattern was observed in CS16-HTG: 25% of VLN-treated and 13% of placebo-treated patients reported an event in the Hypersensitivity SMQ. Excluding events at the injection site, erythema was the most common event reported among VLN-treated patients (6% versus none in the placebo group).

Although not classified as a serious AE by the applicant, a 58-y/o man in CS6-pivotal 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. This led to an ER visit, discontinuation of VLN, dermatology consultation, and treatment with steroids, antihistamines, and eventually cyclosporine. See the narrative in Section 6.4.3.

Table 54. TEAE Hypersensitivity SMQ – CS6-pivotal

	Placebo N=33	**VLN N=33**	**Placebo**	**VLN**
	n (%)	**n (%)**	***Events***	***Events***
Patients with Hypersensitivity SMQ	**6 (18)**	**12 (36)**	**9**	**102**
Erythema	3 (9)	6 (18)	3	8
Pruritus	2 (6)	3 (9)	2	5
Rash	1 (3)	3 (9)	1	3
Urticaria	0	3 (9)	0	6
Injection site urticaria	0	2 (6)	0	64
Eczema	0	1 (3)	0	1
Eosinophilia	0	1 (3)	0	1
Immune thrombocytopenic purpura	0	1 (3)	0	1
Pharyngeal edema	0	1 (3)	0	1
Seasonal allergy	0	1 (3)	0	2
Sneezing	0	1 (3)	0	1
Wheezing	0	1 (3)	0	9

Source: Dr. Andraca-Carrera

Reviewer Comment: Serious cases of hypersensitivity occurred in non-FCS patients, which were associated with the development of anti-VLN antibodies. It is reasonable to expect that patients with FCS may also experience serious hypersensitivity reactions with VLN treatment.

6.5.2. **Renal-related adverse events**

The following stopping rules for renal function tests were implemented in the phase 3 trials.

In the event of a persistent elevation that was observed over 2 weeks, for any of the 3 criteria below, dosing of a patient with Study Drug may have been stopped temporarily:

- Serum creatinine increase that fulfilled all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN
- Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24-hour
- Estimated creatinine clearance calculated according to the formula of Cockcroft and Gault ≤ 40 mL/min that was confirmed by a 24-hour urine collection

Reviewer Comment: The applicant's renal-related stopping rules were not well-designed. (1) Increases in creatinine from baseline (whether absolute and/or relative) could form a reasonable criterion, but a requirement for creatinine to also exceed an "upper limit of normal" is unnecessary and could lead to a false belief that a substantial increase in creatinine (e.g., 0.5 to 1.0 mg/dL) is not clinically significant. (2) Quantitative urine protein assessment is reasonable, but the applicant failed to measure urine creatinine on spot urine samples; therefore, assessments of proteinuria on spot urine samples are essentially uninterpretable, and 24-hr urine collections are very challenging for patients to perform accurately (prone to both undercollection and overcollection). (3) Estimated creatinine clearance (or eGFR) during the course of a clinical trial will only be meaningfully influenced by changes in serum creatinine, which is already captured in the first stopping rule, in concept; furthermore, requiring confirmation of a reduction in estimated creatinine clearance with a 24-hr urine is both clinically unnecessary and prone to inaccuracy, as mentioned above.

No patients in CS6-pivotal or CS7-OLE met these criteria. In Study CS16-HTG, 2 VLN-treated patients met one of these criteria. One of the patients with a history of type 2 diabetes, hypertension, proteinuria, and renal failure permanently discontinued treatment due to worsening proteinuria. The other patient met stopping criteria for elevation in creatinine, the patient's VLN was temporarily held, and treatment was reinitiated with intervening treatment pauses due to low platelet levels. Baseline creatinine was 1.21 mg/dL, and at Week 8, the creatinine peaked at 2.27 mg/dL. Two doses of VLN were held, and at Week 12, creatinine was 1.59 mg/dL. Improvement was noted at Week 32 with creatinine levels decreased to 1.27 mg/dL. The patient completed the study (total 20 doses of VLN), but elevation in creatinine was not considered resolved until after VLN treatment ended.

A table of treatment-emergent renal-related adverse events reported in Study CS6-pivotal follows. No placebo-treated and 4 VLN-treated patients reported treatment-emergent adverse events related to the kidney.

Table 55. Treatment-emergent renal-related adverse events – CS6-pivotal

	Placebo N=33	VLN N=33
	n (%)	n (%)
Any renal-related adverse event	**0**	**4 (12)**
Blood creatinine increased	0	1 (3)
Blood urea increased	0	1 (3)
Creatinine renal clearance decreased	0	2 (6)
Acute kidney injury	0	1 (3)
Renal cyst	0	1 (3)

Source: Clinical Reviewer's analysis, CS6-pivotal adae.xpt

None of these events were recorded as serious. The adverse event of acute kidney failure in a VLN-treated patient ((b) (6)) was associated with an SAE of dehydration associated with an acute diarrheal illness. Resolution of creatinine elevation (creatinine 2.7 mg/dL on hospital admission; 1.1 mg/dL on day of discharge) occurred with fluid resuscitation, suggesting VLN unlikely to be related to this event. The patient received 3 more doses before voluntarily withdrawing from the study on Study Day 57. The other two patients ((b) (6) , (b) (6)) reported adverse events related to unfavorable changes in renal-related laboratories while treated with VLN.

- Patient (b) (6) , reported 3 adverse events of BUN increased, blood creatinine increased, and creatinine clearance decreased. At baseline, the patient's creatinine was 1.38 mg/dL, BUN was 6.4 mmol/L (1.7-7.8 mmol/L), and creatinine clearance was 96 mL/min. At Week 4, creatinine had increased to 1.93 mg/dL (a 0.55 mg/dL increase from baseline), along with BUN (8.9 mmol/L); at Week 13, creatinine was 2.06 mg/dL. Renal ultrasound and nephrology consult were obtained, but no specific diagnosis was confirmed. The patient's creatinine began to improve at Week 14, after study treatment was discontinued (last dose Study Day 92) due to AE of whole body erythema. Patient was treated with oral steroids and eventually cyclosporine because of erythema. By Week 52, creatinine levels had improved somewhat to 1.76 mg/dL. The patient received a total of 14 doses of VLN during the study.

- Patient (b) (6) randomized to VLN 300 mg/week, had decreased creatinine clearance reported on Study Day 398. At baseline, her calculated creatinine clearance was 60 mL/min. On Day 398 it was 51 mL/min (last dose of VLN was Study Day 358). She completed study CS6-pivotal and received a total of 28 doses. After a 4-month period of treatment (delay due to administrative reasons) she enrolled in CS7-OLE. At the screening for CS7-OLE, this AE had resolved. She is currently being treated in CS7-OLE.

Resolution of laboratory abnormalities occurred with discontinuation of VLN treatment. A causal relationship between VLN and abnormal renal-associated laboratory values reported in these latter two cases cannot be excluded given the temporal association with VLN treatment.

In the CS7-OLE study (4-month safety update), there were 2 patients (1 treatment-naïve, 1 CS6-VLN) with reported albuminuria and 2 patients with proteinuria (1 treatment-naïve, 1 CS6-VLN). None of these events was serious.

In CS16-HTG, 12 (16%) VLN-treated versus 3 (8%) placebo-treated patients reported a renal-related adverse event. A higher incidence of adverse events related to increase urine protein and increased creatinine was noted. None of these events was considered a serious adverse event.

Table 56. Treatment-emergent renal-related events – CS16-HTG

	Placebo N=38	VLN N=75
	n (%)	n (%)
Any renal-related adverse event	**3 (8)**	**12 (16)**
Albuminuria	0	3 (4)
Chromaturia	0	1 (1)
Chronic kidney disease	0	1 (1)
Hematuria	0	2 (3)
Microalbuminuria	0	1 (1)
Nephropathy	1 (3)	0
Proteinuria	0	2 (3)
Renal impairment	1 (3)	0
Albumin urine present	0	1 (1)
Beta 2 microglobulin increased	0	1 (1)
Beta 2 microglobulin urine increased	0	1 (1)
Blood creatinine increased	0	3 (4)
Glomerular filtration rate decreased	0	1 (1)
Urine leukocyte esterase positive	1 (3)	0

Source: Clinical Reviewer's analysis, CS16-HTG adae.xpt

Categorical change in serum creatinine

A categorical analysis of serum creatinine was performed to analyze the proportion of patients with changes from baseline in creatinine values ≥0.3 mg/dL higher than baseline or ≥50% higher than baseline. In study CS6-pivotal, no placebo-treated patients and 4 (12%) VLN-treated patients met these criteria. For one of these 4 patients (Patient (b) (6)), the elevation in creatinine was reported as an adverse event. For 2 of the 4 patients (Patient (b) (6) and Patient (b) (6)), these elevations were transient, occurring at a single time point. None of these elevations led to study treatment discontinuation. A similar pattern was noted in CS7-OLE – 4 (7%) patients had a serum creatinine ≥0.3 mg/dL that was transient and occurred at a single time point and did not lead to treatment pause or discontinuation.

In CS16-HTG, there were 6 (8%) VLN-treated versus 2 (5%) placebo-treated patients with serum creatinine increases of ≥0.3 mg/dL or ≥50% higher than baseline versus none in the placebo group. Creatinine levels increased during treatment and resolved during the follow-up period of treatment. One of these patients (b) (6) had other renal-related adverse events (proteinuria, GFR decreased, beta 2 microglobulin increased).

Changes in urinary protein

As commented above, urine creatinine was not measured in CS6-pivotal or CS16-HTG, and therefore quantitative measures of urinary protein normalized for urinary creatinine could not be evaluated. Urine creatinine began to be measured in the ongoing study CS7-OLE in February 2017; therefore, very small numbers of patients have data available (~15 patients). Of 12 patients with an available baseline urinary albumin/creatinine ratio measurement of <30 mg/g at baseline, 3 patients shifted to a worse category (2 into 30 to <300 mg/g and 1 to ≥300 mg/g). In 8 patients with available measurements, no patients had a urine protein/creatinine ratio that shifted to a worse category (all were <150 mg/g baseline and post-baseline). However, due to the very small numbers of patients with available measurements and lack of comparator group in CS7-OLE, conclusions regarding VLN effect on proteinuria cannot be made reliably.

Reviewer Comment: Small imbalances in renal-related adverse events and changes in renal-associated laboratory values are noted with VLN treatment. None of these events was serious and laboratory abnormalities appear to be reversible with discontinuation of therapy. However, given the small safety database and the association with this class and their potential effects on the kidney, continued monitoring is warranted.

6.5.3. Hepatic-related adverse events

In the Phase 3 studies, there were liver-related laboratory criteria (e.g., varying magnitudes/durations of transaminase abnormalities) that led to drug discontinuation if there was not an alternative explanation for the lab values. No patient in CS6-pivotal or CS7-OLE discontinued drug by protocol-mandated liver-related criteria. Two VLN-treated patients in Study CS16-HTG met a liver-related stopping rule. One event had resolution of elevated enzymes with treatment discontinuation – however, alternative factors such as other medications or alcohol could have contributed to the elevation in transaminases. A summary of the other patient follows.

- Patient (b) (6) a 48-year-old white female with history of hypertension, coronary artery disease, MI, coronary angioplasty, and obesity received a total of 4 doses at the time of stopping due to liver enzyme test results. On Study Day 32, the patient's ALT and AST were 389 U/L (>8x ULN) and 458 U/L and met the stopping rule for liver enzyme elevations. Bilirubin was within normal limits. No new medications, alcohol use were reported. Serology was negative, including hepatitis B surface antigen, hepatitis A IgM antibodies, and hepatitis C antibodies. After discontinuing VLN, liver

enzymes slowly declined. On Study Day 99, ALT and AST were 39 U/L and 53 U/L. Intermittent AEs included mild AEs of vomiting and dark colored urine. Vomiting resolved within 2 days and dark colored urine resolved in 1 month.

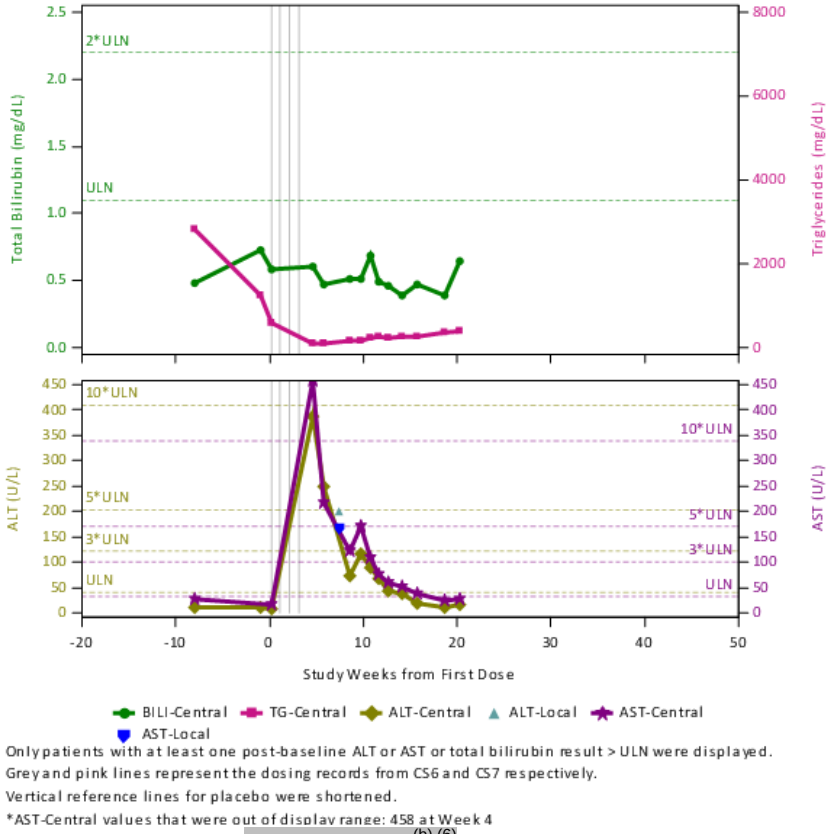


Figure 18. Patient profile (b) (6)

Source: CSR CS16-HTG Patient narrative (b) (6)

Reviewer Comment: Elevation in ALT and AST after four doses of VLN; no increase observed in bilirubin. Given the temporal association with VLN treatment and liver enzyme elevations, a causal association with VLN treatment cannot be excluded.

A total of 5 patients (2 PBO, 3 VLN) in CS6-pivotal reported 7 hepatic-related treatment-emergent adverse events. Three of these events were considered serious (cholangitis, drug-induced liver injury, liver function tests abnormal) and occurred in 2 patients, 1 of whom was a VLN-treated patient. A brief narrative of this patient's event follows the table.

Table 57. Hepatic-related treatment-emergent adverse events – CS6-pivotal

Preferred Term	Placebo N=33	VLN N=33
	n (%)	n (%)
Any hepatic-related adverse event	**2 (6)**	**3 (9)**
Cholangitis	0	1 (3)
Drug-induced liver injury	0	1 (3)

Preferred Term	Placebo N=33	VLN N=33
	n (%)	n (%)
Transaminases increased	0	1 (3)
ALT increased	0	1 (3)
AST increased	0	1 (3)
Hepatomegaly	1 (3)	0
Abnormal liver tests	1 (3)	0

Source: Clinical Reviewer's analysis, CS6-pivotal adae.xpt

- Patient (b) (6) was admitted to the hospital for SAEs of cholangitis and drug-induced liver injury secondary to diclofenac on Study Day 285. The patient's liver enzymes were notable for an ALT of 709 U/L on hospital admission and a peak ALT of 974 U/L (20x ULN), peak AST of 678 U/L (17xULN), peak alkaline phosphatase 1827 U/L (15x ULN), and peak total bilirubin 31 mmol/L (1.8x ULN) during hospital admission. Diclofenac, which had been started 18 days before hospitalization for abdominal pain, was discontinued. The patient was discharged in good condition with cholangitis and drug-induced liver injury after hospital work-up - abdominal pain and fever was adjudicated as "Other" and not pancreatitis. Liver enzyme elevations resolved as outpatient. The patient continued VLN treatment without recurrence of liver-related abnormalities.

The placebo-treated patient (Patient (b) (6) – SAE liver function tests abnormal), experienced elevations in ALT>5xULN, AST>5x ULN, and bilirubin>2x ULN meeting the definition of Hy's biochemical evidence of liver injury. Five days before the abnormal liver function tests, the patient had received a "cinnamon infusion." The SAE of abnormal liver tests was reported. All values resolved without treatment.

An evaluation for instances of categorical elevations in liver enzymes is provided in the table below for CS6-pivotal. Two VLN-treated and 1 placebo-treated patient met the liver enzyme thresholds in the table below.

Table 58. Categorical elevations in liver enzymes – CS6-pivotal

	Placebo N=33	VLN[1] N=33
	n (%)	n (%)
ALT >3x ULN	1 (3)	2 (6)
ALT >5x ULN	1 (3)	1 (3)
ALT >10x ULN	0	1 (3)
AST >3x ULN	1 (3)	1 (3)
AST >5x ULN	1 (3)	1 (3)
AST >10x ULN	0	1 (3)
Total Bilirubin >2x ULN	1 (3)	0
ALT >3x ULN and total bilirubin >2x ULN	1 (3)	0

[1] Table includes patients with values obtained at local labs that met the criteria
Source: Clinical Reviewer's Analysis, adlb.xpt, xb.xpt

The VLN-treated patient with ALT and AST >10x ULN is described above as the patient with drug-induced liver injury. The placebo-treated patient appearing in the above table is described previously as the patient with the SAE of abnormal liver tests.

The other VLN-treated patient (Patient (b) (6)), a 28-year-old female, had an elevation in ALT >3xULN. This patient had a baseline ALT of 29 U/L (range 6-41 U/L) and an ALT of 166 U/L at Week 19. The ALT elevation was associated with a mild AE of "increased transaminases." The patient was noncompliant with treatment (missing 6 doses with no clear explanations) and was discontinued from the study by the Investigator at Week 22. One week after treatment discontinuation, at an unscheduled visit, ALT value was 83 U/L (local lab). No other liver abnormalities were noted.

In CS7-OLE, there were two patients that had ALT>3x ULN, and one patient with ALT >5x ULN. There were no associated increases in bilirubin. The patient with ALT>5x ULN, (b) (6) had a significant elevation in liver enzymes while on placebo treatment in CS6-pivotal (possibly related to cinnamon infusion – see above), which returned to normal values. During CS7-OLE, on VLN treatment, this patient's liver enzymes fluctuated from slightly above normal and elevations >3x ULN (peak ALT 252 U/L week 23). Bilirubin values remained within normal limits. This patient had an ongoing history of steatohepatitis. The other patient ((b) (6)) had a history of hepatic steatosis and chronic liver disease, and had been treated with VLN in CS6-pivotal and enrolled in CS7-OLE. During CS6-pivotal, ALT and AST were normal at baseline (ALT 25 U/L; AST 29 U/L) above the ULN at final visit in CS6-pivotal (ALT 94 U/L, AST 86 U/L); at beginning of CS7-OLE, patient had elevated ALT 138 U/L (3.4x ULN). Liver enzymes were below 3x ULN until Week 43 of CS7-OLE, when both ALT and AST were elevated >3x ULN (ALT 157 U/L; AST 120 U/L); the following week values had decreased (ALT 68 U/L; AST 56 U/L)

In CS16-HTG, there were 12 patients (1 placebo, 11 VLN) reporting 14 treatment-emergent hepatic-related . None of these adverse events were reported as serious.

Table 59. Hepatic-related treatment-emergent adverse events – CS16-HTG

Preferred Term	Placebo N=38	VLN N=75
	n (%)	n (%)
Any hepatic-related adverse event	**1 (3)**	**11 (15)**
Hepatic pain	0	2 (3)
Hepatocellular injury	0	1 (1)
ALT increased	0	1 (1)
AST increased	0	1 (1)
Transaminases increased	0	1 (1)
Hepatic enzyme increased	0	4 (5)
Hepatitis	0	1 (1)
Liver injury	0	1 (1)
GGT increased	0	1 (1)
Hepatic cyst	1 (3)	0

Source: Clinical Reviewer's analysis, CS16-HTG adae.xpt

Two patients (b) (6) (preferred terms hepatitis, liver injury) and (b) (6) (hepatic enzyme increased) were mentioned above for meeting liver-related stopping rules. A third patient, (b) (6), developed hepatocellular injury secondary to serum sickness and was described earlier in the Immunogenicity/Hypersensitivity section. Most of the other events were related to elevations in liver enzymes. The table below summarizes the number and proportion of patients with categorical increases in ALT, AST and bilirubin. No placebo-treated patients exhibited elevations in liver enzymes. No patient exhibited biochemical evidence of Hy's Law. The two VLN-treated patients that met the liver-related stopping rules are included in the category >5x ULN and >10x ULN.

Table 60. Categorical elevations in liver enzymes – CS16-HTG

	Placebo N=38	VLN N=75
	n (%)	n (%)
ALT >3x ULN	0	4 (5)
ALT >5x ULN	0	2 (3)
ALT >10x ULN	0	1 (1)
AST >3x ULN	0	3 (4)
AST >5x ULN	0	2 (3)
AST >10x ULN	0	1 (1)
Total Bilirubin >2x ULN	0	0
ALT >3x ULN and total bilirubin >2x ULN	0	0

Source: CSR CS16-HTG, Table 14.3.4.1.1b.2

6.6. Safety Analyses by Demographic Subgroups

The applicant performed several prespecified subgroup analyses including age, sex, racial, ethnic, and geographic subgroups by pooling the phase 3 studies (CS6 and CS16) and phase 2/phase 3 studies. Given the differences among the studies in patient population, treatment duration, and study treatment allocation, pooled analyses should be interpreted with caution. Several of the subgroup analysis were not informative due to the small number of patients categorized by age, race, or ethnicity even within the pooled group. A high-level review of adverse events in subgroups defined by sex and geographic region in the pooled analyses did not demonstrate meaningful differences.

6.6.1. Pediatrics and Assessment of Effects on Growth

Section 505B(k) of the FD&C Act contains a statutory exemption from the requirement to conduct pediatric studies under PREA for certain drugs with orphan designation ("the PREA orphan exemption"). Under the PREA orphan exemption, PREA does not apply to any application for a drug for an indication for which orphan designation has been granted when that application would otherwise trigger PREA as containing a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration.

No pediatric patients with FCS have been studied with VLN. It is of concern, however, given the typical timing of symptom onset in FCS patients during childhood or adolescence that, if approved, pediatric patients may be treated off-label with VLN despite the lack of characterizing efficacy and safety in this population. Furthermore, the proposed monitoring of platelets every two weeks may be particularly challenging in this patient population.

7. Risk Evaluation and Mitigation Strategies (REMS)

Although a decision on the approvability of VLN has not been made at this time, discussions regarding Risk Evaluation and Mitigation Strategy (REMS) 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. While a REMS with Elements To Assure Safe Use (ETASU) will almost certainly be necessary, it may not be sufficient to ensure that the benefits outweigh the risks, considering the available data. Please see the Division of Risk Management's review for further discussion related to a possible REMS.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL ASSESSMENT OF EFFICACY

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON THE WAYLIVRA NDA

Statistical briefing material for the Waylivra Advisory Committee.
May 10, 2018

Alexander Cambon, PhD
Gregory Levin, PhD/Jennifer Clark, PhD

Division of Biometrics II
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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1 EXECUTIVE SUMMARY

Akcea Therapeutics is seeking approval for Waylivra (volanesorsen sodium - ISIS 304801) for treatment of patients with familial chylomicronemia syndrome (FCS). The proposed indication is as an adjunct to diet for the treatment of patients with FCS.

Brief Overview of Clinical Studies

This efficacy statistical review encompasses two confirmatory placebo-controlled safety and efficacy trials, CS6 and CS16. However only one of the two studies, CS6, includes patients with FCS. Since the indication for this submission is for FCS, this review focuses primarily on this study. Percent change in fasting triglycerides (TG) at 3 months is the primary endpoint for study CS6.

Key Results

There was on average a 77% reduction in triglycerides at 3 months on volanesorsen, as compared to an 18% increase on placebo, for a statistically significant estimated absolute difference in average percent change of -94 percentage points (95% confidence interval: -122, -67). There was also evidence of effects on triglycerides at 6 and 12 months, although estimated effects were smaller than at 3 months (absolute differences versus placebo at 6 and 12 months of -72 and -45 percentage points, respectively, in FDA analyses). This attenuation was likely due to increasing treatment discontinuation on volanesorsen over time. Planned secondary analyses of direct measures of patient benefit such as abdominal pain did not provide any evidence of or show any trends toward a drug effect.

Statistical Issues

1) The Applicant's primary endpoint is percent change in fasting TG from baseline at 3 months. Secondary endpoints include additional TG-related endpoints as well as endpoints related to abdominal pain and acute pancreatitis. TG is a biomarker intended to serve as a surrogate endpoint for symptoms of FCS and risk of pancreatitis. While the primary TG endpoint meets criteria for statistical significance (Section 3.2.3.1), secondary endpoints that directly measure how patients function or feel, such as abdominal pain and acute pancreatitis, do not achieve statistical significance and lack any favorable trend towards the study drug (Section 3.2.3.3).
2) Treatment discontinuation is much higher on the volanesorsen (VLN) arm than on the placebo arm, and this may bias the Applicant's analysis results which rely on likely implausible missing-at-random assumptions.
3) There are more than 80 planned tertiary/exploratory analyses (Section 3.2.1.2) in the Applicant's Statistical Analysis Plan (SAP) and more than 50 additional post-hoc analyses (analyses not pre-specified in the SAP, but included in the Clinical Study Report and/or Report Synopsis, Section 3.2.1.3). These analyses are not included in the hierarchical testing procedure to control Type 1 error. With this many exploratory and post-hoc analyses, it would

be unusual not to find some low p-values, even if there were no treatment effect. See for example Altman, Krzywinski, Nat. Methods 14(1), 2017. Therefore, the results of these exploratory/post-hoc analyses are difficult to interpret—favorable trends may reflect chance findings.

4) Tertiary/exploratory and post- hoc analyses include subgroup analyses of an already very small population. Subgroup analyses such as these can also severely inflate Type 1 error.
5) The blinding of the study may have been inadvertently compromised due to differences in blood plasma color of treated vs. untreated patients, as well as local injection site reactions of treated patients. Unblinding of patients and investigators to treatment assignment could induce bias in analyses of subjective outcomes such as patient-reported measures of abdominal pain and Quality-of-Life Questionnaires such as SF-36 and EQ-5D.

2 INTRODUCTION

2.1 Overview

This submission includes two confirmatory safety and efficacy trials - CS6 and CS16. Study CS2, also included in the submission, is a Phase 2 dose-response study for patients with severe or uncontrolled hypertriglyceridemia. The primary endpoint for both studies CS6 and CS16 is percent change in fasting triglycerides (TG) from baseline to Month 3. However, the study population for CS16 involves patients with severe hypertriglyceridemia, whereas the study population for CS6 involves patients with FCS. In this submission, the Applicant is seeking approval of VLN for treatment of FCS. Primary focus in this review is therefore on Study CS6.

2.1.1 Select Submission History and Communication to Applicant

Comments regarding multiple testing as well as preventing and addressing missing data were communicated to the Applicant on November 4, 2016 (IND 115063, SDN 68) for studies CS6 and CS16.

Comments based on the clinical, clinical outcome assessment (COA), and statistical team reviews were also sent to the Applicant on February 21, 2017. The Agency asked the Applicant to explain the hypothesis concerning the abdominal pain endpoint (for example, if the Applicant expected the effect on abdominal pain severity to occur gradually, to occur rapidly and maintain, or some other pattern), to justify the proposed approach to measure the endpoint, and to explain how frequency would be measured. The Agency also recommended adding 6-month and 12-month efficacy analyses to the statistical hierarchy, and to clarify if the symptom diary in the protocol described the abdominal pain questionnaire.

Pre-NDA comments were sent to the Applicant on Friday June 9, 2017. The Agency advised the Applicant to use an intent-to-treat (de facto) estimand to evaluate treatment effects for primary, key secondary, and subgroup analyses. The Agency also advised the Applicant to account for missing data in a fashion consistent with what the measurement would have been if it had been measured, for example, representing missing data for subjects who did not adhere to therapy from subjects on the same arm who did not adhere to therapy but had the measurement for the endpoint.

2.1.2 Specific Studies Reviewed

Only one study in this submission, CS6, has a study population which includes patients with FCS. Study CS16 has a study population consisting of patients with hypertriglyceridemia. Table 1 gives further details of study design, including background medication and sample size for each of the two studies.

The study population description for CS6 includes “Diagnosis of FCS”. However not all patients in this study had a confirmed diagnosis of FCS. A primary reason for this was the inability to

reproduce/confirm initial lab test results. Please refer to the clinical briefing document of Dr. Mary Roberts for further discussion.

This review focuses primarily on study CS6, since it is the only study that targets FCS patients.

Table 1: Details of Study Design (Source-Reviewer)

Study	Study Design	Treatment Period*	Follow-up Period*	Treatment Arm	Sample Size	Study Population
CS16 (COMPASS) patients with Hypertrigly-ceridemia	MC, MN, R, DB, PG, PC	26 weeks	13 weeks	VLN 300 mg Placebo	75 38	M/F ≥ 18 years Hypertriglyceridemia BMI≤ 45 kg/m^2 at a stable weight (+/- 4 kg) 6 weeks prior to screening, Fasting TG ≥ 500 mg/dL Willing to follow a NCEP ATP III TLC diet, or similar diet with weight maintenance
CS6 (APPROACH) Patients with FCS	MC, MN, R, DB, PG, PC	52 weeks	13 weeks	VLN 300 mg Placebo	33 33	M/F ≥ 18 years History of Chylomicronemia Diagnosis of FCS Fasting TG ≥ 750 mg/dL History of Pancreatitis Willing to follow a diet comprising ≤ 20g fat per day during the study

*All efficacy/ endpoint assessments occur at timepoints during the treatment period; the follow-up period consists of a 13-week post-treatment evaluation period or open label extension study with up to 1 year of treatment.
Abbreviations: FCS- Familial Chylomicronemia Syndrome; MC- multi-center; MN- Multinational; R- randomized; DB- double-blind; PG- parallel group; PC- placebo controlled; VLN-volanesorsen; M/F – Male/Female; TG-Triglycerides; BMI- body mass index; NCEP- National Cholesterol. Education Program; ATP III- Adult Treatment Panel III; TLC- therapeutic lifestyle changes

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The blinding of the study may have been inadvertently compromised due to differences in blood plasma color of treated vs. untreated patients, as well as local injection site reactions of treated patients. Unblinding of patients and investigators to treatment assignment could induce bias in analyses of subjective outcomes such as patient-reported measures of abdominal pain and quality of life.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Study CS6 is a multinational, randomized, double-blind, placebo-controlled, parallel group study comparing VLN to placebo, with a population consisting of patients diagnosed with FCS and willing to follow a diet consisting of < 20g fat daily (Table 1). Please refer to the clinical briefing document of Dr. Mary Roberts for further details and discussion of study design.

The primary and secondary efficacy endpoints for study CS6 are shown in Table 2 and discussed in Section 3.2.1.1. Tertiary/exploratory analyses, which are included in the SAP but not included in the pre-specified multiple testing hierarchy to control Type 1 error, are shown in Table 3 and discussed in Sections 3.2.1.2 and 3.2.3.4. Post-hoc analyses are also shown in Table 3 and discussed in Sections 3.2.1.3 and 3.2.3.4.

3.2.1.1 Primary and Secondary Endpoints

The primary and secondary efficacy endpoints for study CS6 are shown in Table 2. The primary endpoint is percent change from baseline in fasting TG at three months. The value is defined as the average of the Week 12 and Week 13 fasting assessments. If one of these assessments is missing, then the non-missing assessment is used. If both assessments are missing, then the TG primary endpoint for that patient is considered missing. The assessment window for this 3-month endpoint combines the Week 12 and Week 13 assessment windows shown in Section 3.2.1 of the SAP, and is from Day 78 to Day 106. Secondary TG endpoints include percent change from baseline in TG at six months and percent change from baseline in TG at 12 months, as well as responder analyses using cutoffs of TG <750 mg/dL and $\geq$ 40% reduction in TG.

Table 2: Primary and Secondary Endpoints Listed in Hierarchical Testing Order – for Study CS6 (Source-Reviewer)

Endpoint Type	Description
Primary	Percent Change from Baseline in Fasting TG at 3 Months*
Secondary	Fasting TG < 750 mg/dL at 3 Months* (Among Subset with Baseline TG > 750 mg/dL)
Secondary	Percent Change from Baseline in Fasting TG at 6 Months**
Secondary	Percent Change from Baseline in Fasting TG at 12 Months***
Secondary	Average of Maximum Intensity of PR Abdominal Pain During the Treatment Period
Secondary	Percent Change from Baseline in Postprandial TG AUC (0-9 hr).
Secondary	Fasting TG >= 40% Reduction at 3 Months*
Secondary	Change from Baseline in Fasting TG at 3 Months*, 6 Months, and 12 Months
Secondary	Frequency of Composite Episodes of Acute Pancreatitis and PR Abdominal Pain During the On-Treatment Period
Secondary	Change from Baseline in Hepatic Volume

Abbreviations: PR-Patient-Reported;*Average of Week 12 and Week 13 fasting assessments; ** Average of Week 25 and Week 26 fasting assessments; ***Average of Week 50, 51, and 52 fasting assessments.

Since TG is a biomarker, secondary endpoints of abdominal pain and acute pancreatitis, symptoms strongly associated with FCS, are included as secondary endpoints. These are described in more detail below.

Patient-Reported Abdominal Pain Secondary Endpoint

The secondary endpoint of average maximum intensity of patient reported (PR) abdominal pain (5^{th} endpoint in the testing hierarchy) is assessed as follows:

1) Each week patients complete a symptom diary in which they are asked if they had abdominal pain in the last week. If they answer yes, they are asked to report their maximum pain intensity during the previous week on a 0 to 10 numerical rating scale, or NRS (see Figure 1 below).
2) To obtain the average maximum intensity for a patient, these weekly maximum-intensity observations for a patient are averaged over all weeks during the treatment period.
3) Missing weekly maximum intensity observations for a patient are imputed using the next available weekly observation for a patient if there is one available. If there are no non-missing observations available in any of the following weeks for a patient, the observation is ignored (not imputed) in the calculation of the average. This imputation method is given the acronym "NOCB" for "next observation carried backward".
    a. A post-hoc analysis (not specified in the SAP) in the Applicant's report uses zero-imputation (Table 3). In this method, intermediate observations for a patient are imputed as 0. If there are no non-missing weekly observations available in following weeks, the missing observation is ignored, as in the NOCB method.

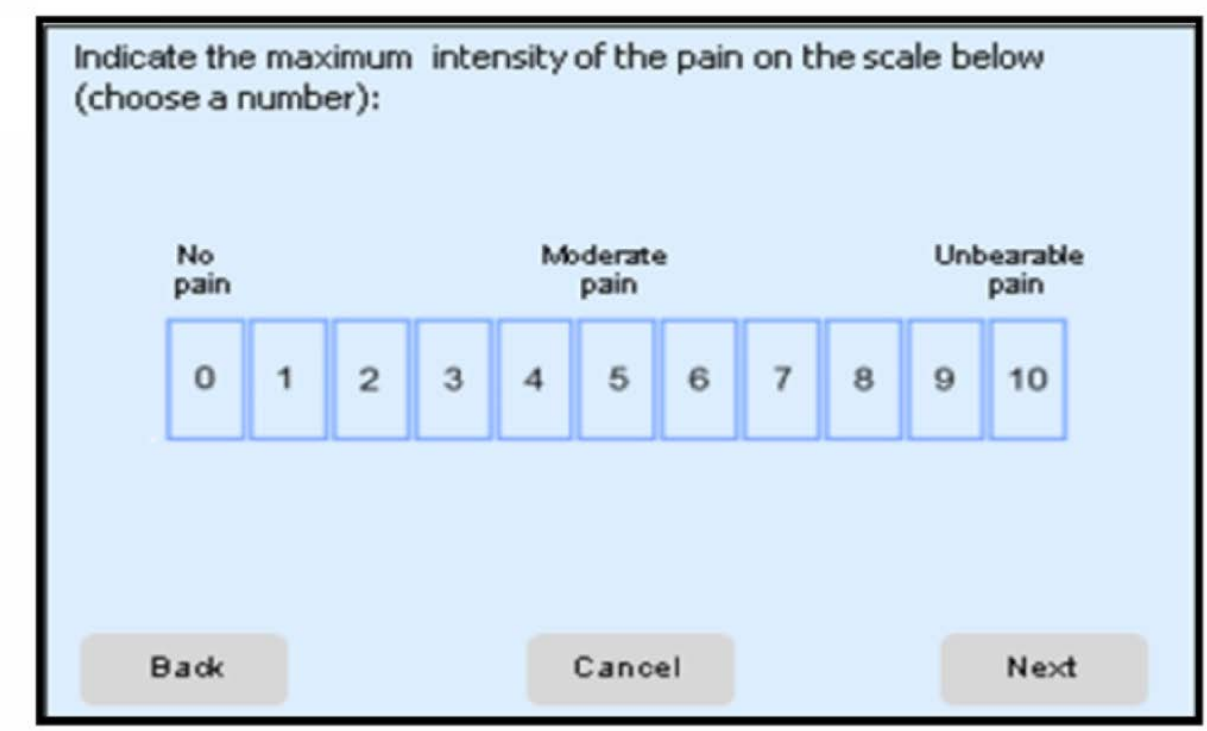


Figure 1: Numerical Rating Scale Instrument-Source- Applicant

Frequency of Composite Episodes of Acute Pancreatitis and Patient-Reported Abdominal Pain

The secondary endpoint of frequency of composite episodes of acute pancreatitis and PR abdominal pain defines as an event an NRS weekly maximum intensity pain score of at least 4, or an adjudicated acute pancreatitis event during the on-treatment period. The NOCB method is used to impute missing data. The "frequency of composite episodes" or yearly rate, is defined in the SAP V2.0 as follows (from Section 3.4.2.6):

> Yearly rate of acute pancreatitis and patient reported moderate or severe abdominal pain (pain score: 4-10) during the on-treatment period, calculated as 365.25 x the number of events during the treatment period/treatment duration, will be summarized with descriptive statistics and p-value from a two-sample test. Acute pancreatitis events will be based on the independently adjudicated pancreatitis data provided by SOCAR. The missing data will be imputed by using NOCB if there is a subsequent score available. Otherwise, the missing data after the last available score of each patient will not be imputed.

However, this explanation for the frequency/yearly rate is unclear. Using information found in footnotes from Table 52 in the Clinical Study Report (CSR), the frequency or yearly rate is defined as the number of the composite events, multiplied by 365.25 and divided by "last dose date – first dose date + 28".

3.2.1.2 Planned Tertiary/Exploratory Analyses

Tertiary/exploratory analyses, which are pre-specified in the SAP but not included in the multiple testing hierarchy to control Type 1 error, are shown in Table 3. This table includes exploratory analyses for secondary endpoints of abdominal pain and/or acute pancreatitis, lipid-related endpoints not included in the primary/secondary endpoints, endpoints for patients with Type 2 Diabetes, planned exploratory analyses for EQ-5D and SF-36 Quality-of-Life Questionnaires, and symptoms related to lipid disorders.

3.2.1.3 Unplanned Post-Hoc Analyses

Unplanned post-hoc analyses are also included in Table 3 below. These are analyses not pre-specified in the Applicant's SAP but that are found either in the Applicant's CSR or report synopsis. These include unplanned analyses related to secondary endpoints of abdominal pain and/or acute pancreatitis, and unplanned subgroup analyses related to EQ-5D and SF-36 Quality-of-Life Questionnaires.

These analyses share the same issue as the tertiary/exploratory analyses in the previous section in that they are not pre-specified in the multiple testing hierarchy to control Type 1 error. Furthermore, these analyses have an additional complication in that they were not even included as planned exploratory analyses in the SAP, and it is unclear how many such post-hoc analyses were conducted.

Table 3: Select List of Tertiary/Exploratory and Post-Hoc Analyses (Source-Reviewer)

Tertiary/Exploratory Analyses Pre-specified in the Statistical Analysis Plan but not Included in the Multiple Testing Hierarchy
Exploratory Analyses for Secondary Endpoints Involving Abdominal Pain and/or Acute Pancreatitis • Same as secondary endpoint for abdominal pain, but using same imputation method used for the primary efficacy endpoint. • Change from Baseline in Average Weekly Max. Intensity of Abdominal Pain in Subgroup Having Any Pain Score >0 During Screening and Week 1 (Using NOCB Imputation) • Change from Baseline in Worst Weekly Max. Intensity of Abdominal Pain in Subgroup Having Any Pain Score >0 During Screening and Week 1 • Uses Abdominal Pain Score >0 in Place of >4 for Composite Endpoint • Yearly Rate of Acute Pancreatitis Events During the Treatment Period • Acute Pancreatitis Event Rate Prior to First Dose of Study Drug, And Treatment-Emergent Events • The Proportion of Patients Having Acute Pancreatitis Event During Treatment Period
Lipid Endpoints, Each Evaluated at 3, 6, and 12 Months • Percent Change from Baseline in Fasting Apolipoprotein B-48 (apoB-48) • Percent Change from Baseline in Fasting Chylomicron-TG • Percent Change from Baseline in Post-Prandial apoB-48 • Percent Change from Baseline in Post-Prandial Chylomicron-TG • Percent Change from Baseline in fasting ApoC-III, Including the Following: o Total ApoC-III o HDL-ApoC-III o LDL-ApoC-III o Chylomicron ApoC-III o VLDL-ApoC-III • Percent change from Baseline in Other Fasting Lipid Measurements, Including: o Non-HDL-C

- ApoB
- HDL-C
- ApoA-1
- VLDL-C
- LDL-C

- Change from Baseline in Lipoprotein Particle Size
- Change from Baseline in Lipoprotein Number
- Percent Change from Baseline in Lipoprotein Particle Size
- Percent Change from Baseline in Lipoprotein Number

Analyses in Patients with T2DM:

- Change from Baseline in Postprandial Glucose
- Change from Baseline in Insulin,
- Change from Baseline in Fasting Glucose
- Change from Baseline in HbA1c
- Change from Baseline in C-peptide

EQ-5D Quality of Life Questionnaire Endpoints, Each Evaluated at 3, 6, and 2 Months

- A shift from Baseline level to post-baseline visit level and the change at post-baseline visit 1 in:
  - Mobility
  - Self-Care
  - Usual Activities,
  - Pain/Discomfort
  - Anxiety/Depression
  - The Health Status Visual Acuity Score (VAS)
  - The Calculated Index Score

SF-36 Quality of Life Questionnaire Endpoints, Evaluated at 3, 6 and 12 Months

- Mean Weighted Scores and Change from Baseline in:
  - Vitality
  - Physical Functioning
  - Bodily Pain
  - General Health Perceptions
  - Physical Role Functioning,
  - Emotional Role Functioning,
  - Social Role Functioning
  - Mental Health

Other Tertiary/Exploratory Endpoints

- Percentage of Patients Who Experienced Eruptive Xanthoma During the Treatment Period
- Counts and Percentages of the Worst Severity of Eruptive Xanthoma
- Yearly Rate During the Treatment Period (365.25 Multiplied by the Number of Events During
- the Treatment Period / Treatment Duration)
- Lipemia Retinalis at Baseline and Week 52 (Odds Ratios)
- Changes from Baseline in Post Heparin Lipoprotein Lipase Mass
- Activity (In Post Heparin Lipoprotein Lipase) Between Treatment Groups
- AUC(0-9hr) of Postprandial Apob-48
- AUC(0-9hr) of Postprandial Chylomicron-TG

Post-Hoc Analyses Not Pre-specified in the Statistical Analysis Plan and not Included in the Multiple Testing Hierarchy

Secondary Endpoints involving PR Abdominal Pain and/or Acute Pancreatitis

- Change from Baseline in Avg. Max. Intensity of PR Abdominal Pain in Patients With Any PR Pain Score >0 During Screening and Week 1 – (Using "Zero" Imputation)
- Number of Patients That Had an Acute Pancreatitis Event During the Treatment Period in Patients With At Least One Prior Event
- Number of Patients That Had an Acute Pancreatitis Attack During the Treatment Period in Patients With At Least Two Prior Events

EQ-5D Quality of Life Questionnaire Endpoints, Evaluated at 3, 6, and 12 Months In Subset of Patients Who Reported Any Abdominal Pain During Screening Period and Week 1

- A shift table comparing baseline level to post-baseline visit levels and the change at post-baseline visit in:
  - Mobility
  - Self-Care
  - Usual Activities
  - Pain/Discomfort

- Anxiety/Depression
- The Health Status Visual Acuity Score (VAS)
- The Calculated Index Score

SF-36 Quality of Life Questionnaire Endpoints, Evaluated at 3, 6 and 12 Months In Subset of Patients Who Reported Any Abdominal Pain During Screening Period and Week 1

- Mean Weighted Scores and Change from Baseline in:
  - Vitality
  - Physical Functioning
  - Bodily Pain
  - General Health Perceptions
  - Physical Role Functioning
  - Emotional Role Functioning
  - Social Role Functioning
  - Mental Health

EQ-5D Quality of Life Questionnaire Endpoints, Evaluated at 3, 6, and 12 Months In Subset of Patients Who Had Pre-dose Adjudicated Pancreatitis

- A shift table comparing baseline level to post-baseline visit levels and the change at post-baseline visit in:
  - Mobility
  - Self-Care
  - Usual Activities,
  - Pain/Discomfort
  - Anxiety/Depression
  - The Health Status Visual Acuity Score (VAS)
  - The Calculated Index Score

SF-36 Quality of Life Questionnaire Endpoints, Evaluated at 3, 6 and 12 Months In Subset of Patients Who Had Pre-dose Adjudicated Pancreatitis

- Mean Weighted Scores and Change from Baseline in:
  - Vitality
  - Physical Functioning
  - Bodily Pain
  - General Health Perceptions
  - Physical Role Functioning,
  - Emotional Role Functioning,
  - Social Role Functioning
  - Mental Health

Abbreviations: Avg.-average; Max. -maximum; PR – Patient-Reported; The screening weeks are used to define the baseline value; -screening weeks are not defined in the SAP;*"Zero" - missing intermediate observations for a patient are imputed as 0; if there are no subsequent observations for the patient, then the missing observation is ignored (not imputed).

Multiple Testing Procedure

A hierarchical multiple testing procedure is used to control the Type 1 error rate at $\alpha \leq 0.025$, one-sided. The order of the hierarchical testing for Study CS6 is shown in Table 2. Tertiary/exploratory endpoints and post-hoc analyses (Table 3) are not included in the hierarchical testing.

3.2.2 Statistical Methodologies

3.2.2.1 Applicant Approach

The Applicant's primary analysis population for the primary endpoint is the Full Analysis Set (FAS): This is defined as all randomized subjects who have received at least one dose of study drug and who have a baseline TG assessment.

The Applicant's defined primary analysis for continuous endpoints involving percent change and change from baseline, including the TG primary endpoint, is an ANCOVA (Analysis of Covariance) model, with the two stratification factors (presence/absence of history of acute pancreatitis and presence/absence of concurrent omega-3 fatty acids and/or fibrates) and treatment group as factors, and log transformed baseline TG as a covariate.

The Applicant's method of imputing missing data for this primary (ANCOVA) analysis utilizes a mixed model which includes baseline TG level, the two stratification factors, and post-baseline TG assessments. Multiple imputation is stratified by treatment according to the method proposed by (Schafer 1997; Schafer 1999). This approach relies on a missing-at-random (MAR) assumption, and treatment discontinuation is not taken into account. Since missing data are strongly associated with treatment discontinuation (Table 4) and any effects of treatment are likely to go away after treatment discontinuation, the MAR assumption is probably not accurate. (See Results and Conclusions, Section 3.2.3.2). More detail on the methodology is reprinted below from Applicant's Statistical Analysis Plan (SAP) V2.0, dated February 3, 2017; there is no revision to this approach in the V2.0 Amendment 1 SAP dated February 28, 2017.

> The imputations will be performed for post-baseline visits. The Markov Chain Monte Carlo (MCMC) method will be used under the multivariate normality assumption to impute the missing primary endpoint by treatment group. The variable list for imputations will include the baseline score, as well as all available post-baseline scores, and stratification factors. To conform to the multivariate normality assumption, baseline, and post-baseline fasting lipid data will be transformed before the imputation process, and the variable values will be back-transformed to create the imputed data set. The SAS procedure PROC MI will be used in the multiple simulation. The MCMC method will impute 100 datasets. EM algorithm will be used to derive a set of initial parameter estimates for MCMC method. A non-informative prior (Jeffreys' prior) will be used to derive the posterior distribution of the parameters.

For the secondary endpoint of average of maximum intensity of PR abdominal pain, the Applicant's primary analysis is a t-test. Week 1 results are not included since they are recorded retrospectively. The following is taken from the Applicant's SAP V2 dated February 3, 2017:

> The maximum intensity of abdominal pain related to disease will be collected on the FCS symptom questionnaire and reported by patients weekly on Bracket electronic patient reported outcomes (ePRO). The average of maximum intensity of patient reported abdominal pain score during the treatment period will be compared between the volanesorsen group and placebo groups using a two-sample t-test. The patients reported results will be mapped to each visit week based on the visit window specified in Section 3.2.1. If patients have multiple results within a visit window, the worst score will be used for summary and analysis. The results recorded during Week 1 will not be included in the treatment period, since the results are reported retrospectively to collect the symptom of patients during the past week. Missing data for any post-baseline visit will be imputed by using Next Observation Carried Back (NOCB) if there is a subsequent score available. Missing data after the last available score of each patient will not be imputed.

A t-test is also specified for the composite secondary endpoint involving both adjudicated acute pancreatitis events and abdominal pain. For both these analyses, intermediate missing data is imputed using the next available observation (NOCB). No imputation is done after the last available measurement for a subject, an approach which relies on an MAR assumption and can inherently introduce bias into the comparative analyses.

For categorical endpoints such as fasting TG < 750 mg/dL at Week 12/13 (among the subset with baseline TG > 750 mg/dL), the primary analysis is defined as a logistic regression model with the two randomization stratification factors and treatment group as factors, and log-transformed baseline triglycerides as a covariate.

3.2.2.2 Statistical Reviewer Approach

For the primary and secondary endpoints, I use the same analysis method as the Applicant (ANCOVA for continuous TG-related endpoints and t-test for abdominal pain and acute pancreatitis-related endpoints). However, my method for addressing missing data for continuous TG-related endpoints is different.

For the TG 6 and 12 Month percent change endpoints, I implement a washout approach in which missing outcomes for subjects on both arms are multiply imputed using a placebo ANCOVA model. In other words, patients who withdraw from the study (and discontinue treatment) on the volanesorsen arm (and the placebo arm) are assumed to have outcomes similar to the observed outcomes on the placebo arm. This approach intends to evaluate the treatment policy estimand, i.e., the difference in average percent change at these time points regardless of adherence. For the categorical TG endpoints, we considered patients who withdrew from the study early to be non-responders—this is considered more appropriate than a missing-at-random assumption, since it is unlikely that patients would be able to maintain TG levels below the target thresholds after treatment discontinuation.

For the secondary endpoints of maximum intensity of patient reported abdominal pain and frequency of composite of acute pancreatitis and patient reported abdominal pain, I use the same method as the Applicant (a t-test). The same approach for missing data is also used. One issue with this approach is that missing data after the last measurement for a patient is ignored. This may introduce bias, since missing data for these endpoints is likely associated with treatment discontinuation in a manner similar to the TG endpoints (Table 4 and Table 9). The mean time (from randomization) of the last non-missing abdominal pain assessment for patients on the VLN arm is significantly less (shorter) than for patients on the placebo arm (see Section 3.2.2.3 for more detail). These issues are addressed in the Results and Conclusions section (Section 3.2.3).

3.2.2.3 Characterization of Treatment Discontinuation and Missing Data

The treatment discontinuation rate was higher in the VLN arm compared to the placebo arm (Figure 2 and Table 4). For the 13-week primary endpoint analysis window (starting at 9 weeks

and 2 days), no subjects had discontinued treatment from the placebo arm, and one subject had discontinued treatment from the VLN arm. By the start of the 26-week analysis window, 8 subjects had discontinued treatment from the VLN arm, while there were still no subjects who had discontinued treatment from the placebo arm. By the start of the 52-week analysis window, 15 subjects (45%) had discontinued treatment from the VLN arm, while only one subject (3%) had discontinued treatment from the placebo arm.

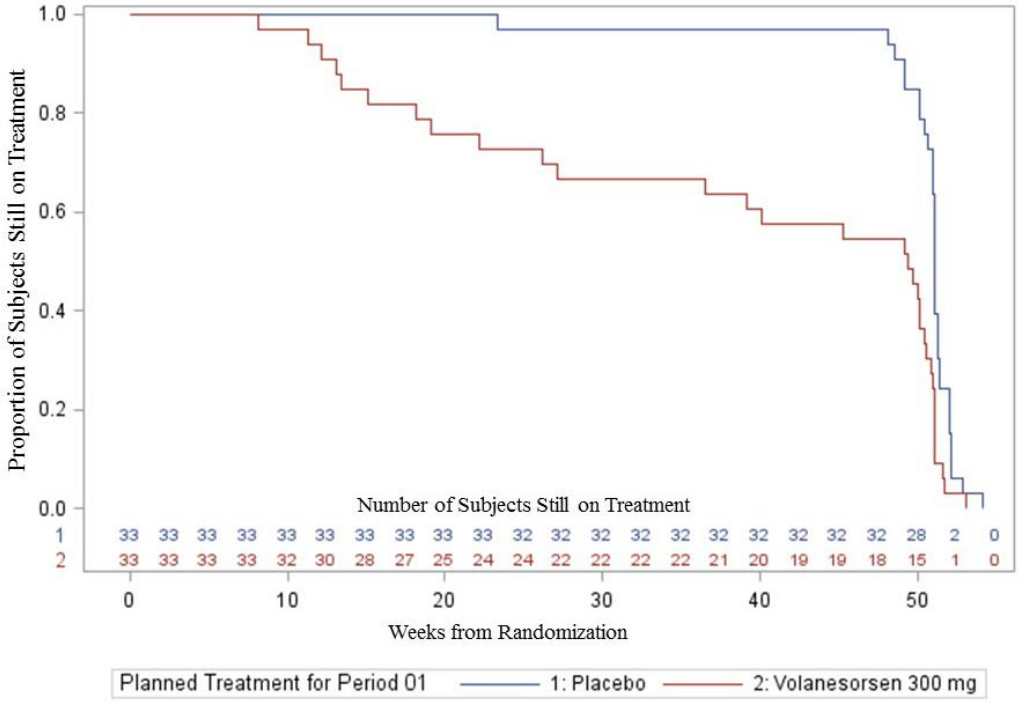


Figure 2: Proportion of Subjects Still on Treatment by Treatment Group During Treatment Period (Source-Reviewer)

Table 4: Descriptive Statistics for Patients Discontinuing Treatment Early and Missing TG Data at 3, 6, and 12 Months (Source-Reviewer)

Time Point	Group	N	Number (Percent) who Discontinued Treatment Early[a]	Number (Percent) with Missing TG Data[b]	Number (Percent) who Discontinued Treatment Early but had TG Data Collected[c]
3 Months	Placebo	33	0 (0%)*	0 (0%)	NA
	Volanesorsen	33	1 (3%)*	0 (0%)	1 (100%)
6 Months	Placebo	33	0 (0%)**	2 (6%)	NA
	Volanesorsen	33	8 (24%)**	4 (12%)	4 (50%)
12 Months	Placebo	33	1 (3%)***	1 (3%)	0 (0%)
	Volanesorsen	33	15 (45%)***	6 (18%)	9 (60%)

a- Number (percent of randomized subjects) of subjects who discontinued treatment before the endpoint assessment window

b- Number (percent of randomized subjects) of subjects who did not have TG data collected on or after the beginning of the endpoint assessment window
c- Number (percent of those who discontinued treatment early) of subjects who discontinued treatment before the assessment window but still had the respective TG endpoint assessment

*Discontinued treatment before 65 days;** Discontinued before 139 days; ***Discontinued before 324 days; cut-off for treatment discontinuation status determined according to analysis window cut point for Weeks 12, 25, and 50, respectively.
Abbreviations: TG-triglycerides; NA-Not Applicable

Follow-up of Patients Who Discontinued Treatment and Still Had Missing Data for Triglycerides

The subject that discontinued treatment on the VLN arm prior to 3 months was followed up to have the primary endpoint assessment. There were no missing TG data in the primary analysis at 3 months. At 6 months, 4 of the 8 subjects who discontinued VLN treatment were followed up to have a TG assessment. For the Month 12 assessment, 9 of the 15 subjects on the VLN arm who discontinued treatment were followed up to have a TG assessment. As a result, there were missing 1-year TG assessments in 6 (18%) of the 33 patients randomized to VLN and 1 (3%) of the 33 patients randomized to placebo.

Missing Data and Treatment Discontinuation for Abdominal Pain, SF-36 and Acute Pancreatitis

On average, the last non-missing weekly maximum intensity of abdominal pain assessment occurred seven weeks earlier on the VLN arm than on the placebo arm (a mean of 45 weeks for the VLN arm vs. 52 weeks for the placebo arm). Figure 3 shows the proportion of missing data (including intermediate missing data) for maximum intensity of abdominal pain in each arm during the screening and treatment period. The proportion of missing data was consistently higher for the VLN group than for the placebo group, and it steadily increased for each group during the treatment period. The pattern is similar to the SF-36 missing data pattern (the missing pattern in Bodily Pain domain score is shown in Figure 4; patterns in other SF-36 domains are identical or nearly so), as well as the missing TG data pattern during the treatment period shown in Table 4. For acute pancreatitis, seven patients on the VLN arm and one patient on placebo arm discontinued treatment early and were not followed up for pancreatitis attacks after treatment discontinuation (source – Applicant response to Agency Information Request dated February 28, 2018).

14.2.21.1.adhoc2.1 Proportion of Subjects with Missing Maximum Intensity Abdominal Pain Over Time with Inconsistent Results Treated as Missing
Full Analysis Set

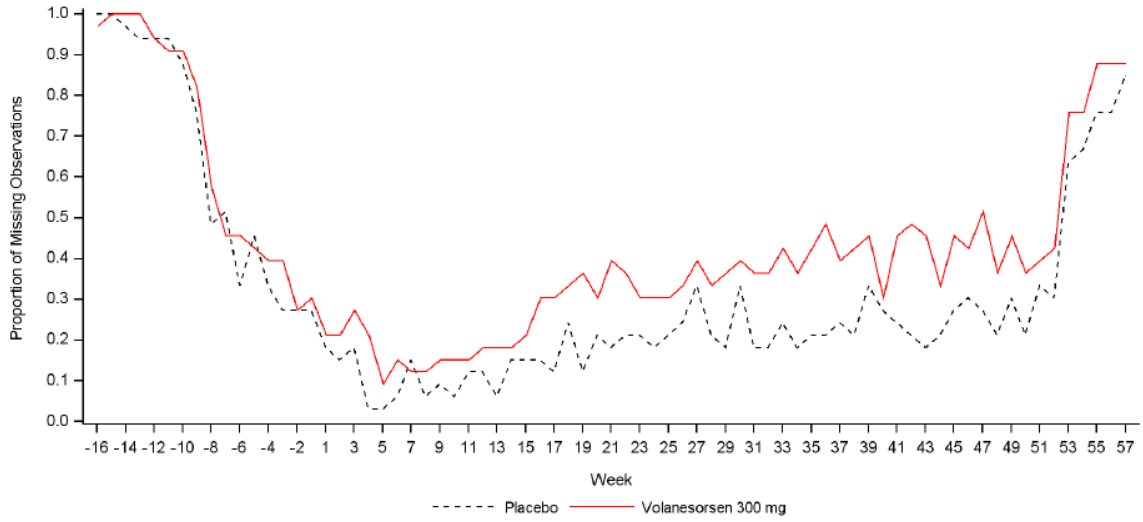


Figure 3: Proportion of Missing Maximum Intensity Abdominal Pain Over Time
(Provided by Applicant in response to Agency Information Request)

Figure 14.2.21.1.adhoc5 Proportion of Subjects with Missing SF-36 Bodily Pain Over Time
Full Analysis Set

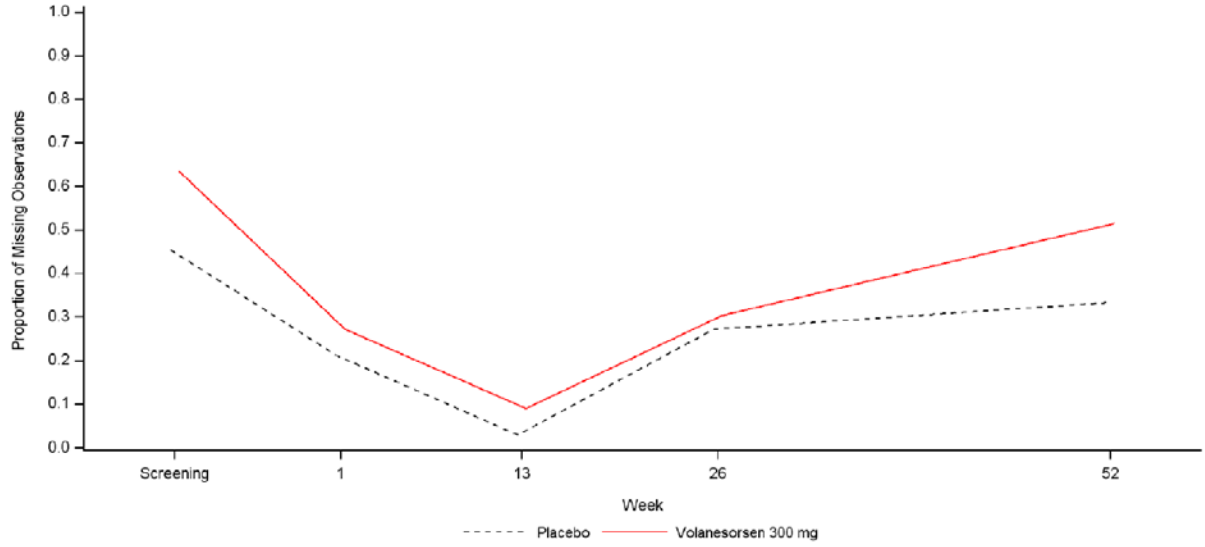


Figure 4: Proportion of Missing Observations for SF-36 Bodily Pain Over Time
(Taken from material provided by Applicant in response to Agency Information Request)

3.2.3 Results and Conclusions

3.2.3.1 Primary Endpoint

For study CS6, the analysis results for the primary endpoint (percent change in TG at 3 months) using the Applicant's ANCOVA method demonstrated superiority (Table 5). Figure 5 shows a large separation in cumulative distribution for percent change in TG at 3 months between the two groups. There was a large and statistically significant treatment effect: there was on average a 77% reduction in triglycerides at 3 months on volanesorsen, as compared to an 18% increase on placebo, for an absolute difference in average percent change of -94 percentage points (95% confidence interval: -122, -67). There is also no missing data at 3 months, so no imputation is necessary.

Table 5: Primary and Secondary Endpoint Results: Percent Change in TG at 3, 6 and 12 Months (Source-Reviewer)

Month	**Placebo (N=33)**		**Volanesorsen (N=33)**		**Mean Difference (95% CI)**	**Mean Difference (95% CI)**
	n	Adjusted Means	n	Adjusted Means	Washout Imputation* Used for 6 and 12 months	Imputation based on MAR assumption**
3	33	17.6	33	-76.5	-94.1 (-121.7, -66.6)	-94.1 (-121.7, -66.6)
6*	31	24.4 *	29	-47.5*	-71.9* (-95.3, -48.6)	-77.8** (-106.4, -49.1)
12*	32	11.9*	27	-32.7*	-44.6* (-70.4, -18.7)	-49.1** (-94.7, -3.5)

*Multiple imputation – missing final assessment values on VLN and placebo arms imputed based on placebo ANCOVA model. ** Source- Applicant Study Report; Multiple imputation – missing final assessment values on VLN and placebo arms based on ANCOVA model. Abbreviations: MAR- Missing at Random.

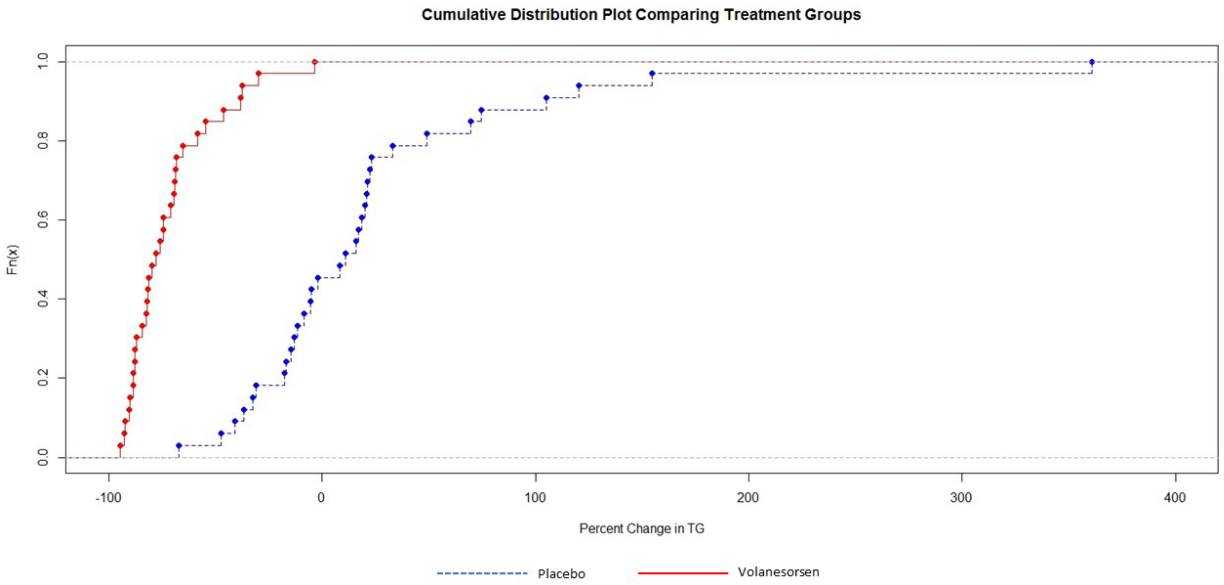


Figure 5: Comparison of Cumulative Distribution of Percent Change in TG Between Treatment Groups at Month 3 (Source-Reviewer)

3.2.3.2 Secondary TG Endpoints

There was evidence of treatment effects on average triglyceride levels at 6 and 12 months, as well as on the proportion of patients meeting certain TG thresholds at 3, 6, and 12 months (Table 5 and Table 6). However, there was attenuation in treatment effects over time. For example, for the 6-month secondary TG endpoint of average percent change, there was some attenuation in the treatment effect relative to the earlier 3-month time point. Given that these analyses include observed data collected after patients discontinued treatment, some of this attenuation may be due to the 4 patients who discontinued VLN treatment but still had non-missing assessments. For the 12-month percent change secondary endpoint, there is further attenuation which may be due to the increased treatment discontinuation over time in the VLN group, and the inclusion in analyses of some TG measurements collected after patients discontinued treatment. More exploration of TG effects over time is given below.

Table 6: Responder Analysis With Non-Responder* Imputation (Source-Team Leader)

TG Threshold	Time	Placebo (N=33) n (%)	Volanesorsen (N=33) n (%)	Unadjusted OR (Exact 95% CI)*
≥20% TG Reduction	Month 3	6 (18.2%)	32 (97%)	144.0 (15.8, 6067.4)
	Month 6	5 (15.2%)	26 (78.8%)	20.8 (5.1, 91.1)

	Month 12	10 (30.3%)	22 (66.7%)	4.6 (1.5, 14.8)
≥30% TG Reduction	Month 3	6 (18.2%)	31 (93.9%)	69.8 (11.4, 679.2)
	Month 6	2 (6.1%)	26 (78.8%)	57.6 (9.8, 555.3)
	Month 12	6 (18.2%)	22 (66.7%)	9.0 (2.5, 33.8)
≥40% TG Reduction	Month 3	3 (9.1%)	29 (87.9%)	72.5 (12.6, 491.0)
	Month 6	1 (3%)	24 (72.7%)	85.3 (10.2, 3613.2)
	Month 12	3 (9.1%)	21 (63.6%)	17.5 (3.9, 103.0)

*Dropouts imputed as non-responders

The Applicant's analysis of the secondary TG endpoints uses an MAR multiple imputation approach assuming those with missing data at months 6 and 12 would behave the same as those who continued in the study. This assumption is not in line with the treatment policy estimand as the treatment effect would likely be overestimated. The overestimation is because we expect those who discontinue VLN to have increased TG levels compared to those who continued treatment. The results in Table 5 reflect this issue, as the Applicant's analyses using the MAR assumption suggested greater treatment effects at 6 and 12 months than analyses using the washout imputation.

Additional Exploration of TG Effects Over Time

In Table 7, descriptive statistics are given for TG levels over time by treatment arm regardless of treatment discontinuation. Table 8 describes the TG levels over time in patients who continue treatment, and Table 9 gives descriptive statistics for TG levels over time for patients who discontinue treatment, including patients who discontinue treatment for a shorter and longer period of time during the treatment period. In Table 8, it can be seen that there is only a slight attenuation from 3 months to 12 months on the VLN arm in patients who are still on treatment at each assessment (difference in percent change of 12.5 from Month 3 to Month 12 for the 18 patients who continued treatment through Month 12). In contrast, Table 9 shows a more pronounced attenuation in patients on the VLN arm who discontinue treatment, and especially for patients who discontinue treatment for a longer period of time before the endpoint assessment. These explorations suggest that increasing treatment discontinuation over time was the primary reason for the attenuated effect on TG over time. The slightly increasing TG levels in patients remaining on VLN suggest the possibility of a declining drug effect over time, although such a change could also be attributable to time trends, dose titration, or chance.

Table 7: Descriptive Statistics for TG at 3, 6 and 12 Months – Percent Change from Baseline for All Subjects Who Had Observed Data (Source-Reviewer)

Month	Placebo (N=33)		Volanesorsen (N=33)	
	n	Mean (SD)	n	Mean (SD)
3	33	24.1 (77.2)	33	-71.8 (20.9)
6	31	25.7 (53.6)	29	-61.5 (34.9)
12	32	14.3 (56.7)	27	-47.4 (41.4)

Abbreviations: SD – Standard Deviation

Table 8: Descriptive Statistics for TG at 3, 6 and 12 Months – Percent Change from Baseline for Subjects Who Were Still on Treatment at Beginning of Assessment Window (Source-Reviewer)

Month	Placebo (N=33)		Volanesorsen (N=33)		Volanesorsen Subjects Who Continued Treatment >= 324 Days (N=18)		6 and 12 Month vs. 3 Month Percent Change for 18 Patients Who Continued Treatment >=324 days
	n	Observed Mean	n	Observed Mean	n	Observed mean	Mean Difference
3*	33	24.1	32	-71.9	18	-73.9	-
6**	31	25.7	25	-62.0	18	-60.0	13.9
12***	32	14.3	18	-61.4	18	-61.4	12.5

For the 6-month endpoint, two patients on the placebo arm were missing the 6 month measurement even though they continued treatment until the start of the treatment window;*treatment duration>=65 days; **treatment duration >=139 days; ***treatment duration >=324 days; Abbreviations: VLN – volanesorsen; Pchg – percent change in TG

Table 9: Descriptive Statistics for TG at 3, 6 and 12 Months – Percent Change from Baseline for Subjects on Volanesorsen Arm Who Continued Treatment vs. Subjects Who Discontinued Treatment After and Before Start of Previous Endpoint Assessment Window (Source-Reviewer)

	Did Not Discontinue Treatment Before Assessment Window*		Discontinued Treatment After Beginning of Prior Assessment Window**		Discontinued Treatment Before Beginning of Prior Assessment Window	
TG Endpoint (Months)	n	Observed Mean	nobs, nmiss	Observed Mean	nobs, nmiss	Observed mean
3	32	-71.9	1, 0	-70.7	-	-
6	25	-62.0	4, 3	-58.2	0, 1	-
12	18	-61.4	5, 2	-33.1	4, 4	-2.5

*Continued treatment to at least the beginning of assessment window for the respective endpoint
**Discontinued treatment, but did continue treatment to the beginning of the previous endpoint assessment window
*** Discontinued treatment, before beginning of the previous endpoint assessment window
Abbreviations: VLN-volanesorsen; nobs – number of subjects with non-missing TG assessment for this endpoint; nmiss- number of subjects missing the TG endpoint assessment; nobs+nmiss is equal to the number of subjects in the category.

3.2.3.3 Secondary Endpoints for Abdominal Pain and Acute Pancreatitis

Results for secondary endpoints related to patient-reported abdominal pain and acute pancreatitis are in Table 10 below. Unlike the primary TG endpoint, which is a biomarker intended to serve as a surrogate endpoint, these secondary endpoints directly measure how patients function and feel. For the abdominal pain endpoint, the means in Table 10 are treatment group averages of the patient-specific average (over the treatment period) of the weekly maximum intensities of pain as measured using the 0-10 NRS scale (see Section 3.2.1.1 for more detail). For the composite endpoint of abdominal pain and acute pancreatitis, the means are the treatment group averages of the number of occurrences, during the on-treatment period, of either a weekly patient reported maximum pain intensity of at least 4, or an adjudicated acute pancreatitis attack; the number of these events for a patient is multiplied by 365.25 and divided by "last dose date – first dose date + 28" to estimate an annual rate.

The results for these two secondary endpoints are not statistically significant in favor of VLN, and there are no positive trends in favor of VLN (Table 10). The means are slightly higher (worse) on the VLN arm than on the placebo arm. The plots of weekly observed maximum intensity of pain (Figure 6) and observed proportions of patients answering no to the abdominal pain question over time (Figure 7) also show no positive trends in favor of the VLN arm. We also know that, at least for endpoints such as TG, missing data are highly associated with treatment discontinuation (Table 4). It is unlikely that if these missing data had been measured, these measurements would have resulted in a more favorable outcome for the VLN arm than that shown in the table.

In addition, since the analysis of the abdominal pain endpoint is not statistically significant, the hierarchical testing procedure (Table 2) stops at this endpoint, and any secondary endpoints below this endpoint in the hierarchy are exploratory in nature (including the endpoint of frequency of composite of episodes of abdominal pain or acute pancreatitis).

Table 10:Secondary Endpoint Results – Abdominal Pain and Frequency of Composite of Episodes of Abdominal Pain and Acute Pancreatitis (Source-Reviewer)

Endpoint	**Placebo (N=33)**		**Volanesorsen (N=33)**		**Mean Difference (95% CI)**
	n	Mean	n	Mean	
Patient Reported Abdominal Pain	33	0.36*	33	0.38*	0.03 (-0.37, 0.42)
Frequency of Composite Episodes of Acute Pancreatitis and Patient Reported Abdominal Pain	33	2.04**	33	2.73**	0.69 (-2.03, 3.42)

Source-Reviewer – consistent with Applicant results found in Report Body; * the average of the weekly maximum intensity of pain, averaged over each patient; NOCB imputation used for intermediate measures; no imputation done for missing data after last non-missing weekly assessment; ** averages of the number of occurrences, during the treatment period, of either a weekly PR maximum pain intensity of at least 4, or an adjudicated acute pancreatitis attack; the number of these events for a patient is multiplied by 365.25 and divided by "last dose date – first dose date + 28".

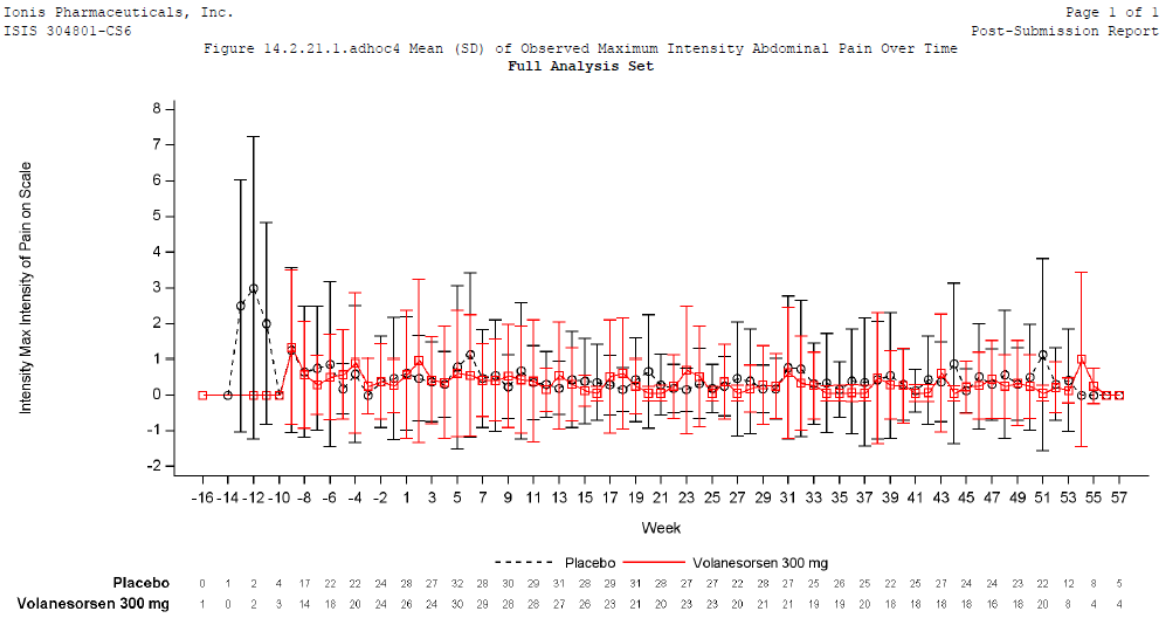


Figure 6: Average of Observed Weekly Maximum Intensity Abdominal Pain Over Time (Source – Applicant)

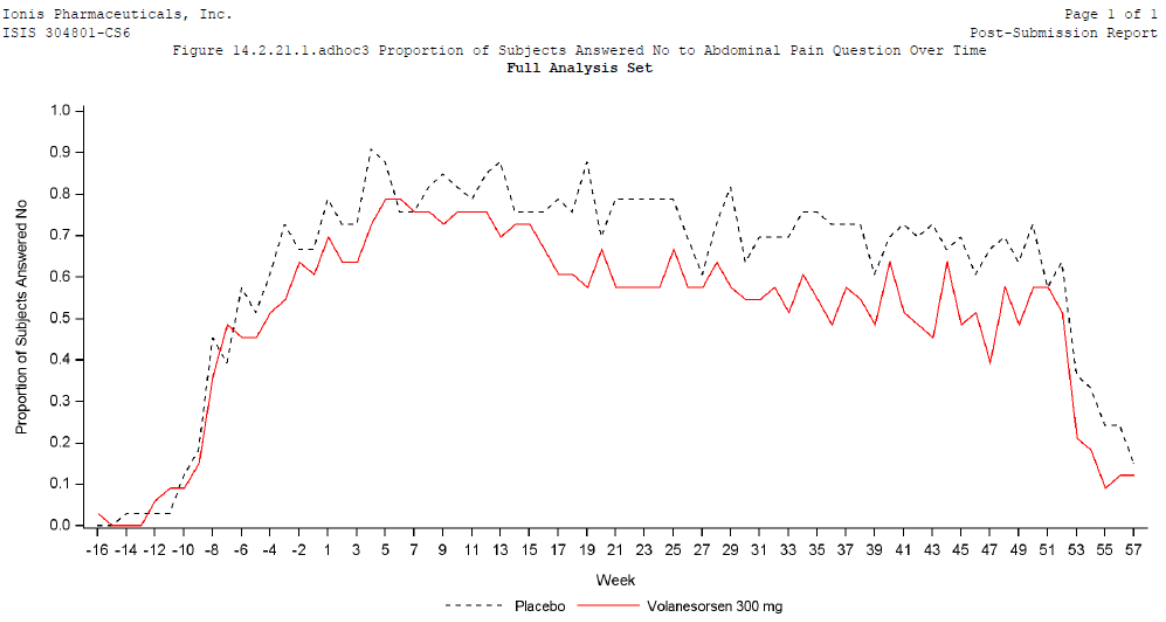


Figure 7: Proportion of Subjects Answering No to Abdominal Pain Question Over Time

Missing Y/N abdominal pain question is imputed by non-missing pain score within the same visit window: Imputed as "No" if pain score equals to 0; imputed as "Yes" if pain score is greater than 0;.the proportion answering "No" was obtained by dividing by 33 (number of patients in group) (Source-Applicant, in response to Agency information request). Note that this method assumes that all those with missing data experienced some pain during that week. More patients on the VLN arm had missing data, so the lower proportion answering "No" on the VLN arm is in part due to this higher missing rate.

3.2.3.4 Tertiary/Exploratory and Post-Hoc Endpoints

Analyses for Acute Pancreatitis Attack

In tertiary/exploratory analyses, the frequency of pancreatitis attacks between treatment groups was compared between all subjects in each group. There was no evidence of a difference in the overall treatment groups, with 3 patients experiencing an attack on placebo versus 1 patient on VLN (Table 11). The Applicant also emphasizes post-hoc (unplanned) analyses comparing pancreatitis rates between treatment arms in the subset of subjects with at least one and at least two prior adjudicated pancreatitis events (also shown in Table 11). Since the population for this disease is already small, evaluating treatment effects using post-hoc analyses in increasingly smaller subgroups is of questionable value. Moreover, the number of exploratory and post-hoc analyses conducted in this study make results from these analyses (likely selected by the Applicant to emphasize based on their results) difficult to interpret – see Statistical Issues Section in Executive Summary.

Another concern is the missing pancreatitis information on the VLN arm due to patients discontinuing treatment. There were disproportionately more patients in the VLN arm that were not followed than in the placebo arm, meaning there was more missing time in which an attack could occur, as can be seen in our information request.

Item #3 in the Agency's Information Request dated February 26, 2018 is reprinted below:

> Clarify how much missing data there were in the analyses comparing the treatment arms with respect to frequency of pancreatitis attacks; for example, provide the number (proportion) of patients on each arm who were not followed for the full 52- week period for the ascertainment of pancreatitis attack information.

The Applicant's response is reprinted below:

> There were 7 volanesorsen-treated patients and 1 placebo treated patient who terminated early from treatment and were not followed for the full 52- week period.

There is substantially more pancreatitis attack information missing on the VLN arm than on the placebo arm. Any observed trends favoring the arm could be in part or in whole due to the fact that more pancreatitis attack information is missing on the VLN arm.

Table 11: Pancreatitis Attacks- Tertiary/Exploratory/Post-Hoc Analysis- Fisher's Exact Test

Type	Group	Placebo	Volanesorsen	Nominal P-Value
Exploratory	**All Subjects, n**	**33**	**33**	
	Had Attack During Treatment Period	3	1	
	No Attack During Treatment Period	30	32	0.61
Post-Hoc*	**Subjects with At Least One Prior Event, n**	**10**	**13**	

	Had Attack During Treatment Period	3	0	
	No Attack During Treatment Period	7	13	0.07*
Post-Hoc	**Subjects with At Least Two Prior Events, n**	**4**	**7**	
	Had Attack During Treatment Period	3	0	
	No Attack During Treatment Period	1	7	0.02

Source-Reviewer – consistent with Applicant Results; *Applicant did not present this p-value in table or report.

Analyses for Abdominal Pain

Table 12 shows specific exploratory and post-hoc analysis results for abdominal pain that were highlighted in the Applicant's application. Subgroup analyses showed some possible positive trends, but there are limitations to these analyses due to their exploratory nature and due to problematic missing data assumptions. For example, the "Zero Imputation" subgroup analysis emphasized by the Applicant was not planned as even an exploratory analysis, and it relies on a missing-at-random assumption for missing data after patient dropout (a questionable assumption given the greater dropout on VLN than placebo; see Figure 3), as well as the likely implausible assumption that missing weekly scores in patients remaining in the study were all zeroes (i.e., none of these patients had any pain during those missing weeks). Any observed trends favoring VLN could be in part or in whole due to random high bias attributable to the post hoc selection of analyses to conduct and to emphasize and/or due to the fact that more abdominal pain information is missing on the VLN arm.

Table 12:Abdominal Pain- Exploratory and Post-Hoc Analysis

Analysis	Placebo		Volanesorsen		Mean Difference (95% CI)
Overall Population Analysis	N	Mean	N	Mean	
Worst Maximum Intensity	33	2.70	33	2.33	-0.37 (-1.98, 1.24)
Subgroup Analyses in Patients with Pain>0 During Screening and Week 1	N	Mean Change from Baseline	N	Mean Change from Baseline	
Average of Maximum Intensity Using NOCB for Intermediate Missing Values	10	-1.97	7	-2.53	-0.57 (-1.21, 0.07)
Average of Maximum Intensity Using Zero Imputation for Intermediate Missing Values (Reviewer)	10	-1.92	7	-2.30	-0.38 (-1.06, 0.30)
Average of Maximum Intensity Using Zero Imputation for Intermediate Missing Values	10	-1.33	7	-2.28	-0.95 (-1.75, -0.16)

Source-Applicant unless otherwise noted

SF-36 and EQ-5D Quality of Life Questionnaires

Results for the SF-36 and EQ-5D instruments are presented in Table 13 and Table 14. For each instrument and each domain, higher scores represent a better health state or status than lower scores. There were no consistent trends favorable towards VLN. In addition, these analyses suffer

from the same potential bias as the TG, acute pancreatitis, and abdominal pain analyses due to greater discontinuation and missing data on the VLN arm.

Table 13: SF-36 Domains - Change from Baseline* -Source-Applicant

Domain	Month	Placebo (N=33)		Volanesorsen (N=33)		Mean Difference (95% CI)
		n	Adjusted Mean	n	Adjusted Mean	
Physical Functioning						
	3	25	-1.50	24	-1.31	0.19 (-3.67, 3.29)
	6	21	-1.90	19	-1.52	0.38 (-3.88, 4.63)
	12	18	-1.28	15	-3.57	-2.29 (-6.68, 2.09)
Vitality						
	3	25	-0.32	24	0.58	0.90 (-3.23, 5.03)
	6	21	0.25	19	0.51	0.26 (-5.07, 5.58)
	12	18	0.22	15	-0.47	-0.69 (-6.00, 4.61)
Bodily Pain						
	3	25	0.47	24	0.37	-0.09 (-4.74, 4.55)
	6	21	0.88	19	-0.86	-1.74 (-6.73, 3.26)
	12	18	1.47	15	-0.01	-1.48 (-7.87, 4.90)
Physical Role Functioning						
	3	25	-0.94	24	0.23	1.17 (-3.18, 5.51)
	6	21	0.01	19	-0.25	-0.27 (-4.22, 3.68)
	12	18	-2.03	15	-4.00	-1.96 (-8.71, 4.78)
General Health Perceptions						
	3	25	2.21	24	-0.03	-2.24 (-6.07, 1.60)
	6	21	1.67	19	1.68	0.01 (-4.86, 4.88)
	12	18	2.28	15	-0.84	-3.11 (-7.87, 1.65)
Social Role Functioning						
	3	25	-0.56	24	1.01	1.57 (-2.72, 5.86)
	6	21	0.69	19	-2.08	-2.77 (-8.77, 3.23)
	12	18	0.60	15	-1.06	-1.66 (-6.24, 2.93)
Emotional Role Functioning						
	3	25	-1.56	24	0.17	1.73 (-2.10, 5.56)
	6	21	-1.10	19	-1.16	-0.06 (-4.42, 4.30)
	12	18	-0.93	15	-2.14	-1.21 (-8.25, 5.83)
Mental Health						
	3	25	0.40	24	0.46	0.05 (-4.62, 4.73)
	6	21	0.89	19	-0.57	-1.46 (-6.81, 3.89)
	12	18	1.98	15	-0.98	-2.96 (-9.44, 3.52)

Table 14:EQ-5D Domains - Change from Baseline -Source-Applicant

	Month	Placebo (N=33)		Volansesorsen (N=33)		Mean Difference (95% CI)
		n	Adjusted Mean	n	Adjusted Mean	
Mobility						
	3	25	0.20	24	0.16	-0.04 (-0.37, 0.30)
	6	20	0.28	19	0.08	-0.20 (-0.65, 0.25)
	12	18	0.06	14	0.42	0.35 (-0.22, 0.92)
Self-Care						
	3	25	0.13	24	0.12	-0.01 (-0.32, 0.30)
	6	20	0.20	19	0.05	-0.15 (-0.58, 0.28)
	12	18	0	14	0	0 *
Usual Activities						
	3	25	0.20	24	0.25	0.04 (-0.34, 0.43)
	6	20	0.22	19	0.19	-0.04 (-0.50, 0.43)
	12	18	0.11	14	0.29	0.17 (-0.08, 0.43)
Pain/Discomfort						
	3	25	0.20	24	0.04	-0.16 (-0.55, 0.24)
	6	20	0.24	19	0.12	-0.12 (-0.62, 0.37)
	12	18	0.06	14	-0.01	-0.07 (-0.37, 0.23)
Anxiety/Depression						
	3	25	0.08	24	0.25	0.18 (-0.10, 0.46)
	6	20	0.11	19	0.25	0.14 (-0.19, 0.46)
	12	18	0.05	14	0.08	0.04 (-0.29, 0.36)
The Health Status VAS						
	3	25	-1.74	24	-5.77	-4.03 (-11.65, 3.59)
	6	20	-5.10	19	-1.90	3.20 (-8.82, 15.22)
	12	18	-0.97	14	2.10	3.06 (-4.40, 10.53)
The Calculated Index Score						
	3	25	-0.044	24	-0.022	0.022 (-0.052, 0.097)
	6	20	-0.063	19	-0.029	0.034 (-0.083, 0.151)
	12	18	-0.010	14	-0.048	-0.039 (-0.100, 0.023)

*For the Self Care domain, all the observed values in the VLN group had the value 1 at Baseline and at Week 52.
Abbreviations: VAS- Visual Acuity

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Because of the small sample size for the CS6 study, any subgroup analyses will be severely underpowered. In the US subgroup, there are only six patients on the placebo arm and five on the VLN arm (Table 15). In addition, Asian and Hispanic/Latino subgroups have very small sample sizes, and there are no Black/African Americans included at all. Given the small numbers, there is large uncertainty in the subgroup estimates; however, there is no evidence that the TG treatment

effects in the Asian, Hispanic, Age, Sex, or US subgroups are substantially different from the overall TG treatment effect shown in Table 5.

Table 15: TG – Percent Change from Baseline at 3 Months in Subgroups -Source-Reviewer

Subgroup	Placebo (N=33)		Volanesorsen (N=33)		Mean Difference (95% CI)
	n	Adjusted Mean*	n	Adjusted Mean*	
Male	14	17.8	16	-76.2	-94.0 (-151.0, -37.0)
Female	19	9.9	17	-80.2	-90.1 (-114.2, -66.0)
Age ≥ 65	2	16*	3	-80*	-95 (-, -)
Age < 65	31	18.1	30	-76.4	-94.5 (-124.2, -64.6)
White	29	15.3	24	-78.1	-93.4 (-127.5, -59.4)
Asian	4	24	7	-74	-98 (-144, -51)
Hispanic/Latino	7	-6	7	-72	-65 (-84, -47)
US	6	74	5	-86	-160 (-346, 25)
Non-US	27	8.6	28	-70.1	-79.2 (-99.3, -58.5)

*Adjusted Mean from linear model

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There is convincing evidence that there is a substantial TG effect due to VLN at three months. There were no missing data at this time point, and my results are consistent with the Applicant's results. There is also evidence of effects on the secondary TG endpoints at 6 and 12 months, although there is some attenuation in the effect over time, much of which is likely due to increasing discontinuation of treatment over time in the VLN arm.

Since the primary TG endpoint is a biomarker intended to serve as a surrogate, supportive analyses of direct measures of how patients function or feel, such as patient-reported abdominal pain, frequency of acute pancreatitis attacks, and quality of life, were considered important to help evaluate the effectiveness of VLN. However pre-specified secondary analyses of the maximum intensity of abdominal pain averaged over the treatment period and of the frequency of the composite outcome of abdominal pain and acute pancreatitis did not show any evidence of a treatment effect, nor any favorable trends for VLN. Furthermore, exploratory analyses of EQ-5D and SF-36 Quality-of-Life scores also did not suggest any trends toward benefit. The Applicant emphasized some favorable trends in analyses in very small subgroups that were either planned exploratory analyses of exploratory endpoints or completely unplanned. Such analyses are considered exploratory in nature and it is difficult to determine whether the trends represent chance findings.

The blinding of the study may have been inadvertently compromised. Unblinding of patients and investigators to treatment assignment could induce bias in analyses of subjective outcomes such as patient-reported measures of abdominal pain and quality of life.

5.2 Collective Evidence

Evidence for efficacy of VLN rests primarily on percent reduction in triglycerides. There is no evidence for efficacy in secondary endpoints not related to TG (specifically abdominal pain and acute pancreatitis). It is difficult to determine if the lack of observed effects on direct measures of patient benefit is due to the small sample size or short duration of the study, or due to lack of efficacy of the drug on these endpoints.

CLINICAL PHARMACOLOGY REVIEW
Office of Clinical Pharmacology

Prepared by Yunzhao Ren, MD & PhD, Lian Ma, PhD, and Jayabharathi Vaidyanathan, PhD

Executive Summary

Volanesorsen is a 20-mer phosphorothioate antisense oligonucleotide inhibitor targeting apolipoprotein C-III (apoC-III) protein synthesis. Like other second generation 2'-O-methoxyethyl (2'-MOE) antisense oligonucleotide (ASO) products, elimination of volanesorsen in the plasma is mainly driven by vast distribution to the peripheral tissues. Clinical studies demonstrate a dose-dependent and time-dependent reduction of mean apoC-III and triglyceride serum concentrations by volanesorsen. A dose-dependent and time-dependent mild to moderate reduction of mean platelet count following treatment with volanesorsen has also been observed. In addition, there were 8 cases of severe thrombocytopenia (<50,000/μL) reported from clinical studies. The platelet reduction effect has been reported with some other second generation ASOs in the literature. Although there is an apparent trend that lower platelet nadir value is associated with lower body weight, the relationship between drug clearance and platelet nadir value is weak. A dosing regimen switch from once weekly to biweekly post-Week 13 appears to have had little short-term effect on mean triglyceride serum concentration and blood platelet count.

Biopharmaceutics

Throughout the clinical program of volanesorsen, there was only one formulation developed. The to-be-marketed formulation is identical to that used in the Phase 3 clinical trials. The drug product used in the Phase 1/2 studies were presented as vials whereas the drug product used in the Phase 3 studies (to-be-marketed) were presented as pre-filled syringes.

Highlights of Pharmacokinetics (PK)

- **Absorption:** Following a single dose subcutaneous injection of 300 mg volanesorsen, there is an initial phase of rapid decline of plasma concentration after maximal plasma concentration is reached approximately 4 hours (Figure 1). After 24-hour post-dose, the plasma concentration reduces to approximately 5% of the C_{max}. Afterwards, volanesorsen plasma concentration declines slowly as the plasma concentration is approximately 1% of C_{max} value at the end of one week. The absolute bioavailability of volanesorsen following a single subcutaneous administration is 79%. There is little to no accumulation of C_{max} and AUC following once weekly dosing regimen. The steady state of C_{trough} appears to have been reached approximately between Week 13 and Week 20 following once weekly dosing regimen (Figure 8). Volanesorsen PK is similar between healthy subjects and patients with familial chylomicronemia syndrome.

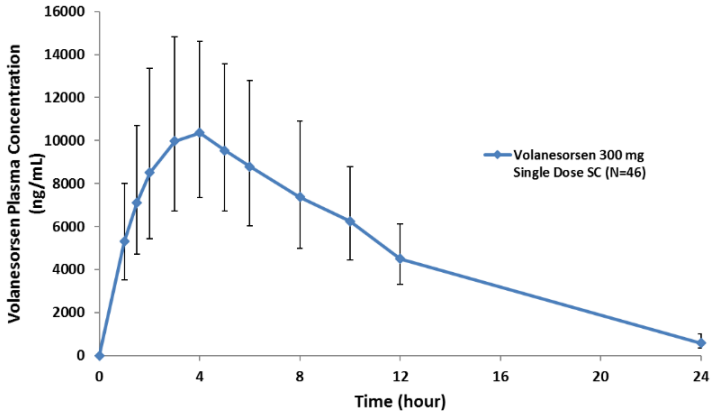


Figure 1 Volanesorsen geometric mean (±SD) plasma concentration-time profile following 300 mg single dose SC injection (Source: adapted from CSR CS13 page 47, Figure 7)

- **Distribution:** The estimated apparent steady-state volume of distribution (Vss/F) by popPK analysis is 251 L. Volanesorsen is highly bound to human plasma proteins (>98%) and the binding is concentration independent. In monkeys, the hepatic concentration of volanesorsen is approximately 20-fold higher than the plasma concentration. In rats, the bone marrow concentration is approximately 70% of hepatic concentration.

- **Metabolism:** Volanesorsen is metabolized in tissues by endonucleases to form shorter oligonucleotides that are then substrates for additional metabolism by exonucleases. Volanesorsen is not a substrate for CYP metabolism. Unchanged volanesorsen is the predominant circulating component in plasma.

- **Elimination:** The typical clearance of volanesorsen is 1.85 L/hr as estimated by population PK analysis. The elimination of volanesorsen involves both metabolism in tissues and excretion in urine. Urinary recovery of the parent drug was limited in humans with < 3% of the administered subcutaneous dose recovered within 24 hours post dose.

- **Intrinsic or Extrinsic Factors:** A population PK analysis with data pooled from six Phase 2 (CS1, CS2, CS4, and CS13) and two Phase 3 studies (CS6 and CS16) suggests that mild and moderate renal impairment has no clinically relevant effect on the systemic exposure of volanesorsen. No data are available in patients with severe renal impairment. The PK of volanesorsen in patients with hepatic impairment is unknown. Based on the population PK analysis, age, sex, or race, has no clinically relevant effect on volanesorsen exposure. The median clearance of volanesorsen decreases 20% from the fourth body weight quartile (109.6 kg as median value) to the first body weight quartile (63.4 kg as median value) (Figure 2). Similarly, the median clearance of volanesorsen decreases 16% from patients ≥ 70 kg (median body weight of 90 kg, N=204) to <70kg (median body weight of 61 kg, N=52).

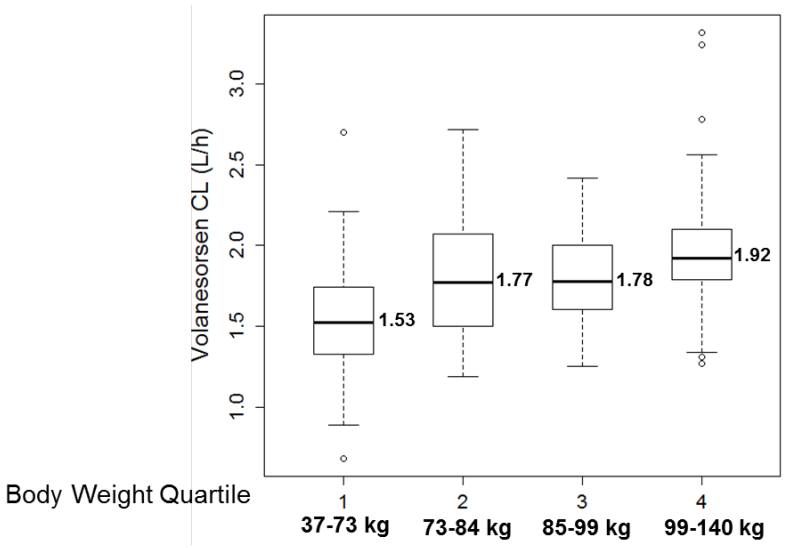


Figure 2 Boxplot of volanesorsen CL (L/hr) over baseline body weight quartiles. The median body weight of each quartile is 63.4, 78.3, 90.5, and 109.6 kg, respectively. (Source: Reviewer's analysis).

Based on in vitro studies, volanesorsen did not induce or inhibit major CYP450 enzymes. It is also not a substrate of drug transporters such as OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP. No clinically relevant drug-drug interactions are identified by population PK analysis between volanesorsen and common co-medications in patients with hypertriglyceridemia.

Highlights of Immunogenicity

- **Overall immunogenicity incidence:** Immunogenicity was evaluated in all Phase 2 and 3 studies. Following a once weekly dosing regimen in Study CS2, CS6, and CS16, the antidrug antibody (ADA)-positive incidence is 3%, 54%, 17%, and 18% in placebo, 100 mg, 200 mg, and 300 mg group, respectively (Table 1). There were only 2 subjects from placebo group being positive for ADA at pre-treatment baseline. 96% of ADA-positive volanesorsen-treated subjects remained persistently positive. The median time of ADA onset (first time being ADA positive) was Day 175 in subjects receiving 300 mg once weekly treatment. Overall, immunogenicity was not associated with either efficacy or safety, however ADA+ did result in minor effects on PK.

Table 1 Immunogenicity Results Summarized from Studies CS2, CS6, and CS16 (safety Set)

Study	Treatment	ADA+ Incidence	Pre-dose ADA+ Incidence	Persistent[1] ADA Incidence	Median Day of the first ADA+ sample
CS2	Placebo	0% (0/24)	0%	-	-
	100 mg	54% (7/13)	0%	100% (7/7)	175
	200 mg	17% (4/23)	0%	100% (4/4)	102
	300 mg	7% (2/28)	0%	100% (2/2)	177

CS6	Placebo	3% (1/33)	100% (1/1)[2]	0% (0/1)	1
	300 mg	30% (10/33)[3]	0%	90% (9/10)	180
CS16	Placebo	5% (2/38)	50% (1/2) [2]	50% (1/2)	25
	300 mg	16% (12/75)	0%	100% (12/12)	165
All	Placebo	3% (3/95)	67% (2/3)	33% (1/3)	1
	100 mg	54% (7/13)	0%	100% (7/7)	175
	200 mg	17% (4/23)	0%	100% (4/4)	102
	300 mg	18% (24/136)	0%	96% (23/24)	176

[1] Persistency is defined as all the ADA samples were positive from the first day of positive results during the study. The persistent ADA+ also includes patients only showing positive result with the last ADA sample collected.
[2] The titer of pre-dose ADA+ samples were 1:50 (the lowest listed titer).
[3] There was one more subject reported as ADA+ in the 4-month safety update which is not included here.
Source: summary-clin-pharm.pdf, page 82, Table 19.

- **Effect of immunogenicity on PK:** Because the total plasma concentration of volanesorsen was measured, there is approximately 3-fold increase of median value in ADA-positive $C_{trough,ss}$ compared to ADA-negative $C_{trough,ss}$.

- **Efficacy of immunogenicity on efficacy:** Generally, there was no consistent effect of ADA status on impairment of efficacy (i.e., triglyceride reduction) at the individual level.

- **Efficacy of immunogenicity on safety:** Although numerically more ADA+ patients in the volanesorsen treatment group discontinued study, there was no consistent effect of ADA status on platelet reduction at the individual level.

Highlights of Pharmacodynamics (PD)

The sponsor conducted a Phase 2 dose ranging Study CS2 in patients with severe or uncontrolled hypertriglyceridemia. Study CS2 was a randomized, double-blind, placebo-controlled, parallel group study. There were 4 planned groups (Table 2). Enrolled patients were to receive a total of 13 doses of once weekly study drug. A total of 96 patients were planned for Groups 1, 2, and 3. Group 4 was open-label dose group planned in patients with FCS (up to 6 patients planned to be enrolled). Subjects were required to have baseline fasting triglyceride serum concentration ≥ 440 mg/dL without triglyceride-lowering therapy and ≥ 225 mg/dL on a stable well-controlled dose of fibrate, for at least 30 days prior to screening.

Table 2 Groups of Patients Enrolled in Study 304801-CS2

Patient Group	Arm	Description	Study Treatment Cohorts
Group 1	Monotherapy	Patients not receiving any additional (i.e., background) TG-lowering therapy	Placebo or ISIS 304801 100, 200, or 300 mg
Group 2	Monotherapy	Patients not receiving any additional (i.e., background) TG-lowering therapy	Placebo or ISIS 304801 100, 200, or 300 mg
Group 3	Fibrate combination	Patients on a stable dose of fibrate (i.e., background) therapy	Placebo or ISIS 304801 200 or 300 mg
Group 4	FCS	Patients with Fredrickson Type 1 dyslipidemia	ISIS 304801 300 mg

Source: from CSE, page 53-54, Table 11

Study CS2 demonstrates a dose-dependent and a time-dependent reduction of mean serum target protein, apoC-III, by volanesorsen from 100 mg to 300 mg once weekly treatment (Figure 3A). The steady state of serum apoC-III reduction appears to be reached at approximately Week 11 to 13. At the end of Month 3, the apoC-III mean percentage change from baseline was 4.2%, -40%, -63.8%, and -79.6% following placebo, 100 mg, 200 mg, and 300 mg volanesorsen treatment, respectively.

A dose-dependent and a time-dependent reduction of serum triglyceride is also observed in the same patient population (Figure 3B). The steady state of serum triglyceride reduction appears to be reached approximately at Week 9. At the end of Month 3, the mean serum triglyceride percentage change from baseline was 20.1%, -31.3%, -57.7%, and -70.9% following placebo, 100 mg, 200 mg, and 300 mg volanesorsen treatment, respectively. By a simple E_{max} model, the estimated IC_{50} values for serum apoC-III reduction and triglyceride reduction from baseline is 246 mg and 184 mg, respectively.

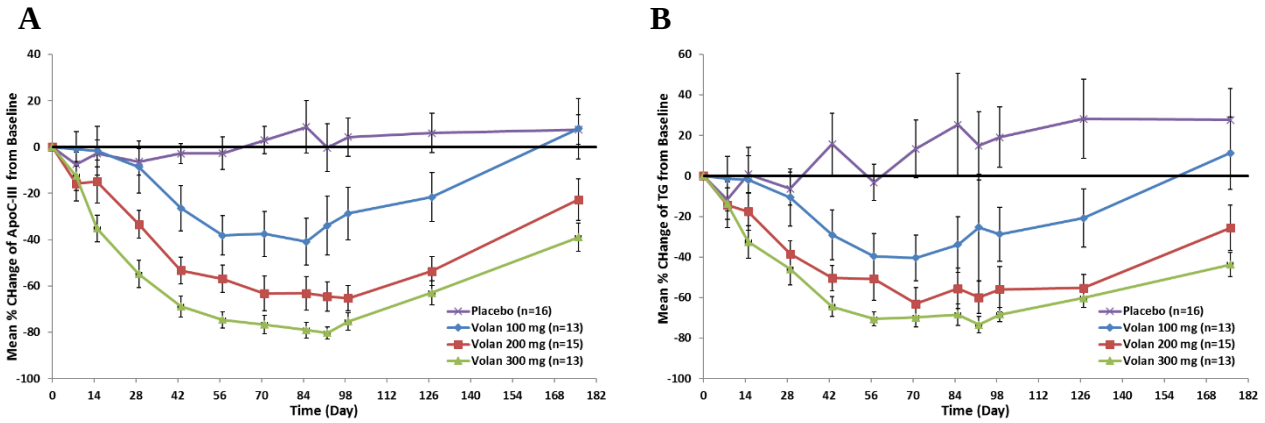


Figure 3 Effects of volanesorsen on (A) fasting apoC-III mean % change from baseline and (B) fasting triglyceride mean % change from baseline in Groups 1 and 2 (monotherapy arm) from Study CS2. (Source: adapted from CSR CS2, page 80, Figure 3; and page 84, Figure 5)

A dose-dependent and a time-dependent reduction of mean blood platelet count from baseline is also observed in the same Study (Figure 4). The blood platelet count at baseline was 226, 242,

217, and 221 $\times 10^3/\mu L$ in placebo, 100 mg, 200 mg, and 300 mg volanesorsen group, respectively. At the end of Month 3, the mean platelet count percentage change from baseline was 4.5%, -14.2%, -16.2%, and -23.9% in placebo, 100 mg, 200 mg, and 300 mg volanesorsen group, respectively. Note, that the steady state of platelet reduction does not appear to be reached during 13-week treatment period.

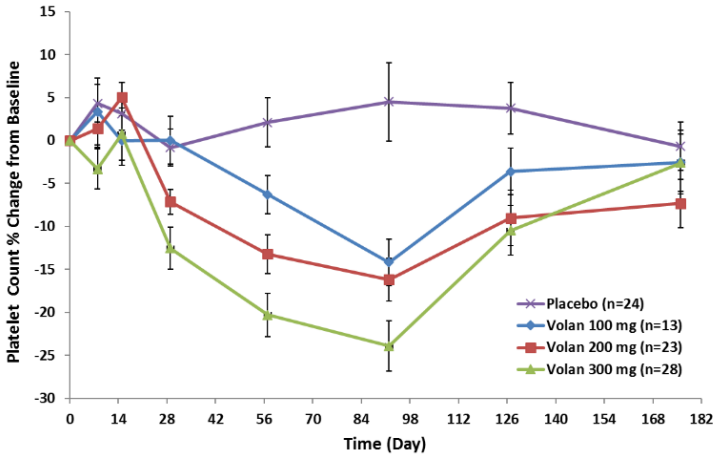


Figure 4 Effects of volanesorsen on blood platelet count mean percentage change from baseline from Study CS2 (safety set). (Source: adapted from CSR CS2, page 149, Figure 17)

Based on results from this dose ranging study, 300 mg volanesorsen administered once weekly was selected to move forward in the Phase 3 studies CS6 and CS16. The planned treatment of Study CS6 was placebo or 300 mg volanesorsen once weekly for 52 weeks. The initial planned treatment of Study CS16 was also placebo or 300 mg volanesorsen once weekly for 26 weeks. Later, Study CS16 Protocol Amendment 4 indicated that all patients would have dose frequency reduced to 300 mg every 2 weeks after 13 weeks of treatment (exemptions would be made for patients who had completed ≥ 5 months of treatment as of 27 May 2016) to lessen the chance of platelet reduction.

Phase 3 study CS6 demonstrated that following 300 mg once weekly treatment, the steady state of mean platelet count reduction is reached approximately at Week 32 with approximately 37% reduction from the baseline in patients who completed study (N=19). (Figure 5A). The absolute mean platelet count was lower than the lower boundary of the normal range (150,000/μL) after Week 32 (Figure 5B).

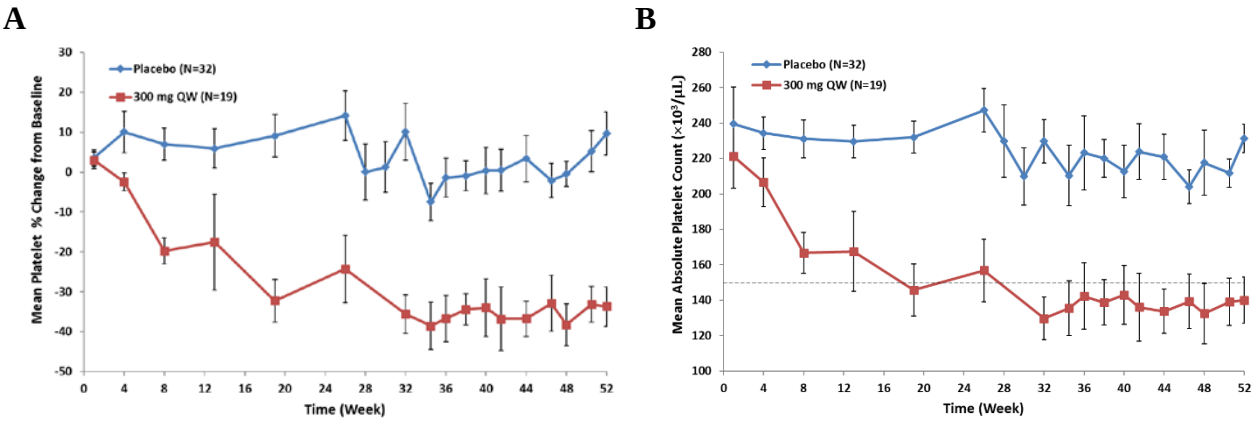


Figure 5 Time profiles of mean percentage change from baseline (A) and absolute values (B) of blood platelet count in patients completed Study CS6. Every point represents mean value from at least 10 subjects. (Source: Reviewer's analysis)

Other than the dose-dependent and time-dependent reduction of population mean platelet count which stabilized at approximately two-thirds of the baseline level after Week 32, there were individual cases who experienced grade 3 (<50,000/μL) and grade 4 (<25,000/μL) thrombocytopenia. With submission date as cutoff (08/30/2017), there were 8 subjects that experienced grade 3 (<50,000/μL) and grade 4 (<25,000/μL) thrombocytopenia. The thrombocytopenia event-related and demographic information of 8 subjects is summarized in Table 3.

Table 3 Severe Thrombocytopenia Event (≥ Grade 3) Related Information in 8 Subjects

Study	ID #	Gender	Age (year)	Body Weight (kg)	Clearance (L/h)[1]	Baseline Platelet Count[2]	Platelet Nadir Count[2]	First Day of Thrombocytopenia[3]	Treatment at Thrombocytopenia[4]
CS2	(b) (6)	Male	57	68	2.19	101	49	92	Once weekly
CS6		Female	56	52	1.43	184	40	92	Once weekly
CS6		Male	43	111	1.92	210	8	257	Once weekly
CS6		Female	48	56	1.83	247	15	135	Once weekly
CS16		Male	55	89	1.54	176	41	51	Once weekly
CS7		Female	68	42	N/A	277	28	155	Biweekly
CS7		Female	31	62	N/A	238	22	80	Once weekly
CS7		Female	45	N/A	N/A	213	42	78	Biweekly

[1] The median volanesorsen clearance is 1.74 L/h from population PK analysis
[2] as in 10^3/μL
[3] as < 50,000/μL
[4] All patients started with 300 mg once weekly treatment
[5] The subject switched to 300 mg biweekly treatment after first time platelet count <100,000/μL on Day 70 and discontinued study when platelet count <50,000 on Day 155. The subject was reported to have hepatitis A on Day 76.
[6] The subject switched to 300 mg biweekly treatment after first time platelet count reached 101,000/μL on Day 57 and discontinued study on Day 71 when platelet count reached 80,000/μL.
Source: Reviewer's summary

All 8 patients except ID# (b) (6) were diagnosed as FCS. All but two subjects (ID# (b) (6) and (b) (6)) experienced severe thrombocytopenia (< 50,000/μL) during the once weekly treatment period. Both subjects (ID# (b) (6) and (b) (6)) switched from once weekly to biweekly regimen due to low platelet counts (≤ 100,000 /μL); and all their platelet count nadir value reached < 50,000 /μL during the biweekly treatment period. There is no consistent demographic pattern (age, body weight, baseline platelet count) correlated with the severe thrombocytopenia, nor is drug clearance. The first time to event is quite unpredictable and not well-aligned with Week 32 maximum-reduction stabilization time line. In one case (ID# (b) (6)), the platelet count dropped from <100,000/μL to <50,000/μL in as short as 2 weeks. The platelet count patterns of these patients after dose interruption or termination were also different. The platelet count of one patient (ID# (b) (6)) returned to the normal level after approximately a 2-month treatment pause and remained >100,000 /μL after the treatment resumed. However, the platelet count of another patient (ID# (b) (6)) dropped below 50,000/μL the second time after the treatment resumed.

Due to the inconsistent patterns in thrombocytopenia observation above, it is understood that the sponsor could not develop a longitudinal population PK/PD model to adequately describe the time course of platelet decline and recovery in these 8 patients. According to the sponsor, attempted models failed to capture low platelet counts especially for patients with nadir platelet counts <25,000/μL.

Highlights of Exposure-Response

Because only one dosing level (300 mg) was investigated in Phase 3 studies, the exposure-response analysis did not reveal a clear relationship between observed volanesorsen C_{trough} and serum triglyceride percentage reduction from baseline at Week 13 (Figure 6). A steeper relationship between observed C_{trough} and serum triglyceride reduction within Week 13 is probably due to time-dependent increase of mean C_{trough} till Week 13 (when C_{trough} steady state is reached) and time-dependent reduction of mean triglyceride till Week 9 (when triglyceride reduction steady state is reached).

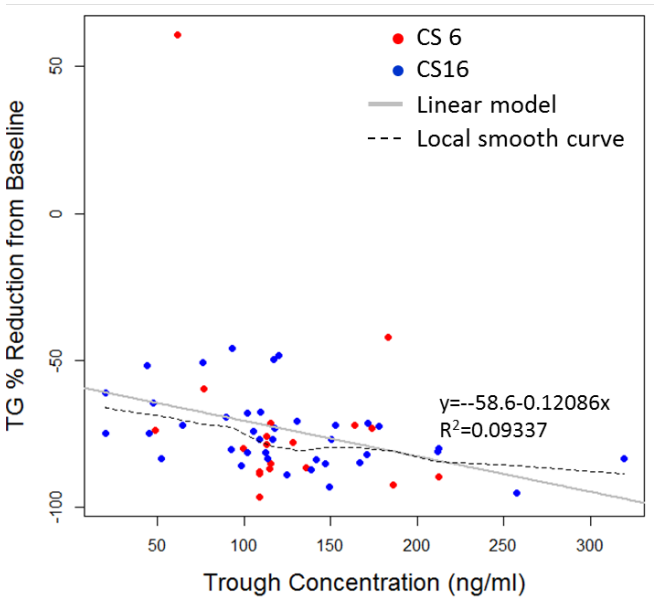


Figure 6 Scatter plot of observed triglyceride % change from baseline and volanesorsen plasma trough concentration at Week 13 combined from Studies CS6 (red points, N=19) and CS16 (blue points, N=39) (PK data set). 57 patients received volanesorsen dose at Week 12. Patients with positive ADA results at Week 13 are excluded (N=4). (Source: reviewer's analysis)

Similarly, the exposure-response analysis did not reveal a clear relationship between observed volanesorsen C_{trough} and platelet reduction value at Week 13 (Figure 7). Instead, the sponsor claims there is a weak relationship between the estimated C_{trough} at Week 13 and the platelet nadir values obtained through the study. This weak relationship could be confounded by many factors, such as patients whom discontinued study earlier may have very low estimated C_{trough} at Week 13 and their platelet count values tend to be high due to the short period of treatment (Figure 5 indicates the steady state of platelet reduction not being reached till Week 32).

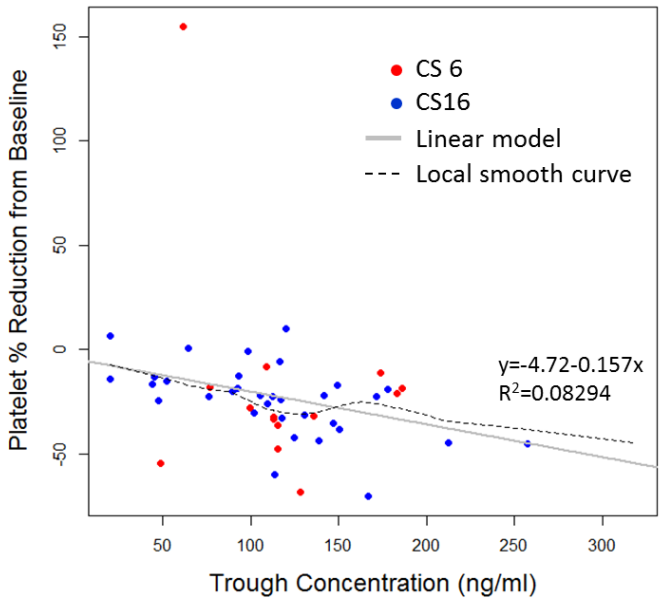


Figure 7 Scatter plot of observed platelet count % change from baseline and volanesorsen plasma trough concentration at Week 13 combined from Studies CS6 (red points, N=19) and CS16 (blue points, N=38) (PK data set). 56 patients received volanesorsen dose at Week 12. Patients with positive ADA results at Week 13 are excluded (N=4). (Source: reviewer's analysis)

Highlights of Dosing Regimen Adjustment

To mitigate the potential severe thrombocytopenia adverse events, the sponsor proposed that volanesorsen is contraindicated in patients with baseline platelet count lower than 140,000/μL. In addition, based on patients' body weight and their platelet counts during the treatment, the following dosing regimen adjustment and platelet monitoring plan is proposed (Table 4).

Table 4 Proposed Volanesorsen 300 mg Dosing Regimen

Platelet Level*	Dose Adjustments		Platelet Monitoring
	Body Weight < 70 kg	**Body Weight ≥ 70 kg**	
Normal (≥140)	Starting dose: once weekly for 3 months, biweekly thereafter	Once Weekly	Biweekly
100-140	Biweekly	Once Weekly	Biweekly
75-100	Biweekly	Biweekly	Once Weekly
50-75	Pause, resume biweekly when ≥100		Twice per week until stable
<50	Pause, resume biweekly when ≥100		Daily until stable
<25	Discontinue Waylivra		Daily until stable

* $\times 10^3/\mu L$

Of note, this body weight-based and platelet count-dependent dosing scheme (regimen adjustment and treatment resumption condition) was not pre-specified in the study protocols and hence not investigated in volanesorsen clinical development program.

Switching from once weekly to biweekly dosing regimen post-Week 13 was investigated in Study CS16 in patients with hypertriglyceridemia. In this study, about 2/3 of patients were scheduled to switch from once weekly dosing regimen to biweekly dosing regimen post-Week 13 due to Protocol Amendment 4. The effect of this dosing regimen switch on PK, efficacy (i.e., triglyceride reduction), and safety (i.e., platelet counts) is evaluated here. Due to the relatively high discontinuation rate, observed results only from study completers are summarized.

- **PK assessment**

In study completers who were on 300 mg volanesorsen once weekly dosing regimen, volanesorsen mean C_{trough} steady state appears to be reached approximately at Week 13 to 20 (Figure 8). In study completers who were on volanesorsen treatment and switched to a 300 mg biweekly dosing regimen exactly after Week 13, the mean C_{trough} values were reduced to approximately one quarter the value of once weekly dosing regimen at Week 19. Since there was little accumulation of C_{max} of volanesorsen after multiple doses from 200 mg to 400 mg in the Phase 1 study, the C_{max} of volanesorsen following biweekly dosing regimen is expected to be the same as once weekly dosing regimen. Also, based on the observation that there is little accumulation of $AUC_{0\text{-}24h}$ after multiple doses from 200 mg to 400 mg, the AUC_τ of volanesorsen following biweekly dosing regimen is expected to be approximately half the value of once weekly dosing regimen.

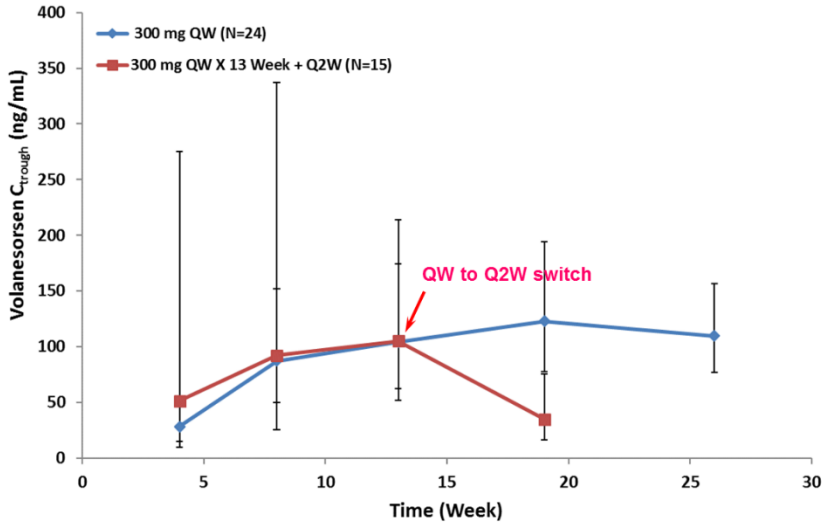


Figure 8 Volanesorsen mean observed plasma C_{trough}-time profiles in patients completed Study CS16. Blue profile represents completers following 300 mg once weekly regimen. Red profile represents completers strictly following 300 mg biweekly post-Week 13 regimen. Only ADA negative samples were included in the plot. (Source: reviewer's analysis)

- **Efficacy assessment**

In study completers who were on volanesorsen treatment and switched to a 300 mg biweekly dosing regimen exactly after Week 13, there was no noticeable impairment of the mean serum triglyceride reduction (% change from baseline) up to Week 25 compared to study completers who were kept on volanesorsen 300 mg once weekly treatment (Figure 9). Beginning from Week 26 when the last dose was administered, there was approximately 10% less reduction of mean triglyceride in biweekly post-Week 13 completers compared to once weekly completers. However, Study CS16 was only conducted for a 26-Week treatment and the long-term effect of dosing regimen switch on triglyceride reduction is unknown.

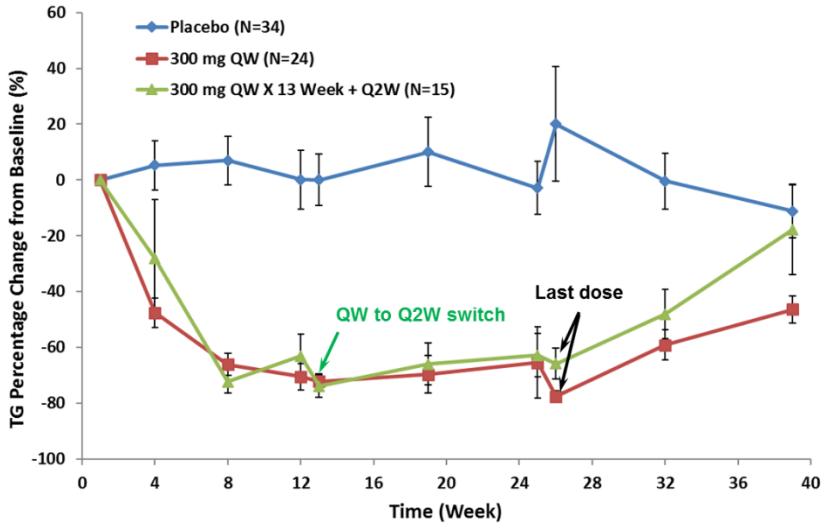


Figure 9 Observed mean (± SE) fasting serum triglyceride % change from baseline over time in patients who completed Study CS16. Blue curve (N=34) represents completers on placebo treatment. Red curve (N=24) represents completers who kept volanesorsen treatment as once weekly regimen. Green curve (N=15) represents completers who switched volanesorsen treatment from once weekly to biweekly exactly post-Week 13 due to Protocol Amendment 4. (Source: Reviewer's analysis).

- **Platelet count assessment**
  In the same study, the mean platelet count change from baseline is also compared in study completers followed volanesorsen once weekly treatment and biweekly post-Week 13 treatment (Figure 10). For an unknown reason, the platelet count percentage change from baseline in completers on biweekly post-Week 13 regimen declined faster than completers on once weekly treatment during the initial 13-week once-weekly treatment period. In study completers who switched to biweekly regimen exactly post-Week 13, their platelet count reached nadir (-30%) at Week 15 and stabilized at approximately at -26% till the end of treatment. In study completers who kept on once weekly treatment, their platelet count reached nadir (-27%) at Week 19 and stabilized till the end of treatment.

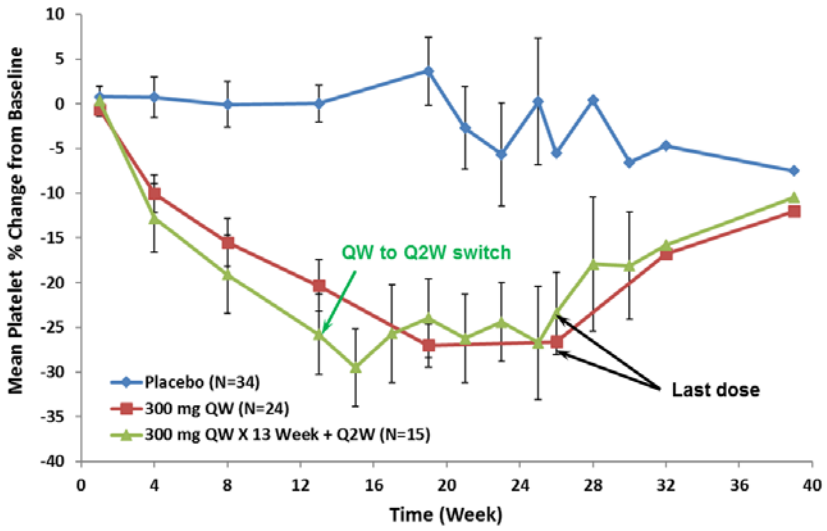


Figure 10 Mean (± SE) of platelet count change from baseline over time in patients who completed Study CS16. Blue curve (N=34) represents completers on placebo treatment. Red curve (N=24) represents completers who kept volanesorsen treatment as once weekly regimen. Green curve (N=15) represents completers who switched volanesorsen treatment from once weekly to biweekly exactly post-Week 13 due to Protocol Amendment 4. Every point represents mean value from at least 10 subjects. (Source: Reviewer's analysis).

According to the results from Study CS6, the steady state of mean platelet count reduction is reached approximately at Week 32 with approximately 37% reduction from the baseline in patients with FCS. In addition, due to the short duration of biweekly treatment period in Phase 3 studies, the long-term effect of biweekly dosing regimen on mean platelet count is unknown.

The proposed dosing regimen recommends patients with body weight <70 kg and normal platelet count (>140, 000/μL) switch from once weekly to biweekly dosing regimen after Week 13. By these criteria, there were only three subjects from Study CS16 who had body weight <70 kg with normal platelet count switched from once weekly to biweekly dosing regimen after Week 13. The individual platelet count-time profiles of three patients are displayed in Figure 11. Although two of these three patients (ID# (b) (6) and ID# (b) (6)) had relatively stable platelet count after the switch from once weekly to biweekly treatment at Week 13, the platelet nadir values were reached post-Week13 in all three subjects. No clear trend in platelet reduction was observed after QW to Q2W switch in patients <70 kg.

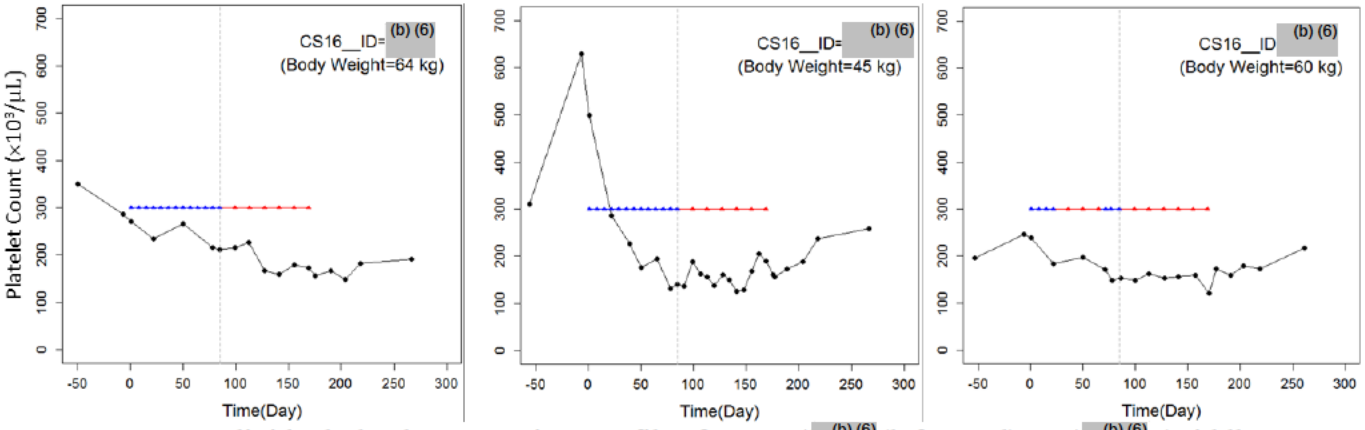


Figure 11 Individual platelet count-time profiles from ID# (b) (6) (left panel), ID# (b) (6) (middle panel), and ID# (b) (6) (right panel) with body weight <70 kg and normal platelet count (>140, 000/μL) that switched from once weekly to biweekly dosing regimen post Week 13 (vertical dashed line) from Study CS16. Blue points and lines correspond to weekly dosing day and dosing interval. Red points and lines correspond to biweekly dosing day and dosing interval. (Source: Reviewer's analysis).

In conclusion, consistent with the published literature on some of the second generation ASOs, there are two types of platelet reduction events observed following volanesorsen treatment. Type 1 is time- and dose-dependent mild to moderate population mean reduction from baseline. In patients with FCS following once weekly treatment, the mean platelet count declined with time and stabilized at Week 32 with approximately 37% reduction from the baseline, which the absolute mean count value (~135,000 /μL) was lower than the lower boundary of the normal range (150,000 /μL). Type 2 is time-independent, severe platelet reduction to <50 $\times 10^3$/μL (mostly with magnitude of >75% reduction), as shown in Table 3. Seven out of the eight patients who experienced severe thrombocytopenia were diagnosed as FCS, which indicates that the interaction between FCS and volanesorsen treatment may be a risk factor of severe thrombocytopenia. The effect of dose on Type 2 platelet reduction is unclear since there was only one incidence reported from the dose ranging Study CS2 and the treatment duration in this study was relatively short (13 weeks). Similarly, the effect of dosing regimen on Type 2 platelet reduction is also unclear due to the small sample size (only 15 patients followed exact biweekly post-Week 13 regimen and completed study) and short treatment duration of 300 mg biweekly regimen investigated in Study CS16. In addition, two patients with FCS (ID# (b) (6) and (b) (6)) in Study CS7 experienced severe thrombocytopenia (< 50,000/μL) after they switched from once

weekly to biweekly treatment when their low platelet counts (≤ 100,000 /μL) were first noticed. All these observed results indicate that switch from once weekly to biweekly dosing regimen might not be an optimal approach to mitigate the risk of severe thrombocytopenia.

The effect of body weight on platelet reduction was evaluated. Although there is an apparent trend showing that patients with lower body weight tend to have lower platelet nadir values upon volanesorsen treatment (Figure 12), the trend may be more representative of a relationship between body weight and Type 1 platelet reduction as several patients who experienced severe thrombocytopenia appear as outliers in the graph (Figure 12). In addition, systemic exposure (AUC) volanesorsen is estimated to be slightly higher (16%) in patients with higher body weight (≥70 kg) than those with lower body weight (<70 kg) at the same dose (Figure 2). The effect of dosing regimen adjustment (double of dosing interval and half of the total dose) based on this 16% change of exposure by body weight remains to be tested without support of sufficient observed data.

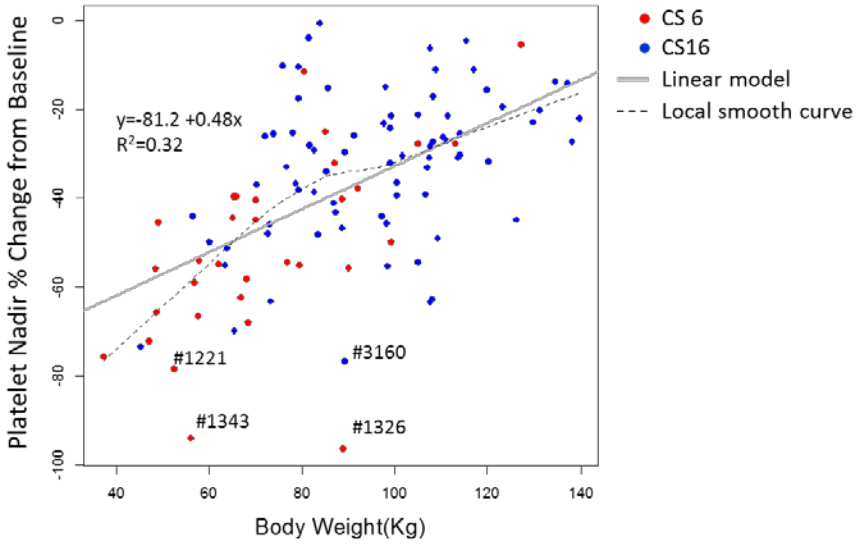


Figure 12 Platelet count nadir value (% change from baseline) over baseline body weight from Studies CS6 (red points, N=33) and CS16 (blue points, N=75). Each point represents one subject. Platelet nadir values from subjects # (b) (6) (b) (6) (b) (6) and (b) (6) are listed in Table 2. (Source: Reviewer's analysis).

FDA Hematology Consult

Qin Ryan, MD, PhD
Division of Hematology Oncology Products (DHP)

Issue: To assess the safety profile, mechanisms and clinical management of thrombocytopenia in patients with familial chylomicronemia syndrome (FCS) exposed to Waylivra in clinical trials

Consult Response:

1. *Division of Metabolism and Endocrinology Products (DMEP) Inquiry:* Provide your assessment regarding the effect(s) of volanesorsen on platelets, including platelet counts and/or platelet function. Discuss the clinical significance of these effects.

   DHP Response: Treatment-related or drug-induced thrombocytopenia occurred in patients treated with volanesorsen. Thrombocytopenia occurred at a greater frequency and severity in patients treated with volanesorsen as compared to placebo. Bleeding events occurred more frequently in patients treated with volanesorsen as compared to placebo. However, bleeding events have occurred in volanesorsen-treated patients in the setting with normal platelet counts which raise the concern for platelet dysfunction as a contributory factor for bleeding.

   The clinical trial data indicated the relative risk of volanesorsen induced thrombocytopenia is 2.8-fold higher than placebo. The incidence of severe thrombocytopenia (platelets $< 50 \times 10^9$/L) was 10%.

   Thrombocytopenia events related to volanesorsen were mostly gradual onset and the majority were reversible.

   Patients with platelet nadir $< 25 \times 10^9$/L were given IV or PO prednisone. One patient with platelet nadir $< 10 \times 10^9$ and active infections was administered IVIG. Some cases were rechallenge positive. Platelet counts observed in placebo controlled clinical trials appear to progressively decrease with longer volanesorsen exposure, regardless of whether study patients have a history of intermittent low platelet at baseline as observed in Gaudet's natural history study of platelet count in patients with familial chylomicronemia syndrome.

   Although minor bleeding events were higher in volanesorsen treated patients in CS6, a relationship between platelet count and the frequency of bleeding events was not identified. Based on the limited available data, thrombocytopenia related bleeding events in volanesorsen trials appear to be mild to moderate. Severe thrombocytopenia associated with potentially life-threatening bleeding consequences have not been identified in the available data provided in this NDA. However, given rechallenge positive events and proposed chronic duration of

treatment, the risk of severe bleeding in the setting of volanesorsen induced thrombocytopenia cannot be excluded at the present time.

2. *DMEP Inquiry:* What is understood regarding the mechanism underlying these effects? What potential mechanisms do you believe have been reasonably excluded? What potential mechanisms, if any, should be the subject of further investigation?

   DHP Response: The applicant's investigation into the mechanisms of volanesorsen induced thrombocytopenia have not identified a root cause of cellular and molecular pathological processes of patient's platelet count decline after volanesorsen exposure.

   Consultation with a hematologist is recommended for patients who develop thrombocytopenia on volanesorsen-treatment. The hematologist can help guide additional tests to be performed for further evaluation and management of thrombocytopenia and bleeding events.

3. *DMEP Inquiry:* Provide any estimates you may be able to make for the anticipated incidence of major or life-threatening hemorrhage related to thrombocytopenia if volanesorsen were approved for Familial Chylomicronemia Syndrome and used according to the applicant's proposed labeling.

   DHP Response: It is difficult to estimate the anticipated incidence of major or life-threatening hemorrhage due to limitations with the small size of the safety database and also with unclear pathophysiology for the thrombocytopenia.

4. *DMEP Inquiry:* What recommendations would you have, if any, regarding the use of concomitant medications among patients treated with volanesorsen (antiplatelet agents, anticoagulants, etc.).

   DHP Response: Aspirin (ASA) was the only concomitant agent of interest found in CS6 trial patients. An exploratory analysis in CS6 trial patients suggested that more volanesorsen recipients on concomitant ASA had bleeding events than those on ASA and placebo, with no statistically significant relative risk. No other concomitant antiplatelet or anticoagulants reported in the randomized trial CS6.

   Patients who require concomitant antiplatelet or anticoagulant therapy should be assessed whether benefits of volanesorsen treatment outweigh the risks of bleeding.

5. *DMEP Inquiry:* The applicant has proposed to mitigate the risk of thrombocytopenia through a REMS that includes a communication plan to healthcare providers with recommendations for dosing and monitoring of platelet counts (see attachment). DMEP and DRISK will be reviewing whether a REMS would be required if this product were to be approved, but we would appreciate any input you would have to inform this assessment as well as any comments on

the adequacy of the applicant's proposed labeling – and the monitoring strategy outlined in their proposed REMS – to mitigate the risk of thrombocytopenia with volanesorsen treatment.

DHP Response: The cases reviewed suggest the frequent platelet monitoring does not prevent severe thrombocytopenia. The thrombocytopenia cases from volanesorsen trials reviewed revealed that frequent or daily platelet monitoring in outpatient setting was difficult to adhere to and likely to be impractical in real world setting. We recommended that patients and prescribers should be informed of the risks of use of the product, including risk of thrombocytopenia and hemorrhage.

In the event of severe thrombocytopenia or hemorrhage, a hematology consult for evaluation and management is recommended.

Appendix

I. Background

Volanesorsen is an antisense oligonucleotide (ASO) designed to inhibit the expression of apo-C-III protein. The submitted NDA is based on one randomized placebo controlled trial in patients with FCS, supported by an open label extension trial in patients with FCS and a randomized trial in patients with High Triglyceride Syndromes (HTG) including familial chylomicronemia syndrome (FCS), as summarized in Table 1 (for additional details please see Dr. Mary Roberts' DMEP clinical review).

Table 1: Key trials supporting volanesorsen NDA

Trial ID	Design	Population	Treatment
CS6	1:1 placebo controlled international study	FCS n=66 (33 per arm)	Volanesorsen 300mg/wk vs placebo, 52 weeks
CS7	Open label extension	70 FCS patients planned, 60 enrolled (cut-off Aug 2017), 43 treatment naïve (30 from CS6, 2 from CS16, 11 new)	Volanesorsen 300 mg/wk up to 104 weeks
CS16	2:1 placebo controlled	HTG n=113 (FCS n = 7, randomized 5 in volanesorsen arm and 2 in placebo arm)	Volanesorsen 300 mg/wk vs placebo for 26 weeks, switch to QOW for > 5 months.

Source: NDA 210645

II. Thrombocytopenia and Related Complications

Drug-induced thrombocytopenia is a well-known adverse event associated with exposure to ASOs in preclinical animal studies and clinical trials. Profiling ASO induced thrombocytopenia indicated there are two types of thrombocytopenia typically observed in ASO clinical trials, as summarized in Table 2.

Table 2: Types of thrombocytopenia observed in ASO trials

Type	Thrombocytopenia	Clinical Presentation
Common	Gradual and slow decline, mild, rarely can be moderate or severe.	Asymptomatic, mild or moderate bleeding may or may not need clinical intervention, mostly reversible.
Rare	Rapid onset, severe.	Rapid onset and severe thrombocytopenia, accompanied with catastrophic and fatal bleeding, irreversible in some cases.

Source: Chi et al., 2017, Limmroth 2014, Drisapersen AC briefing, Powers 2016, Tefferi 2015a, Salloum 2016.

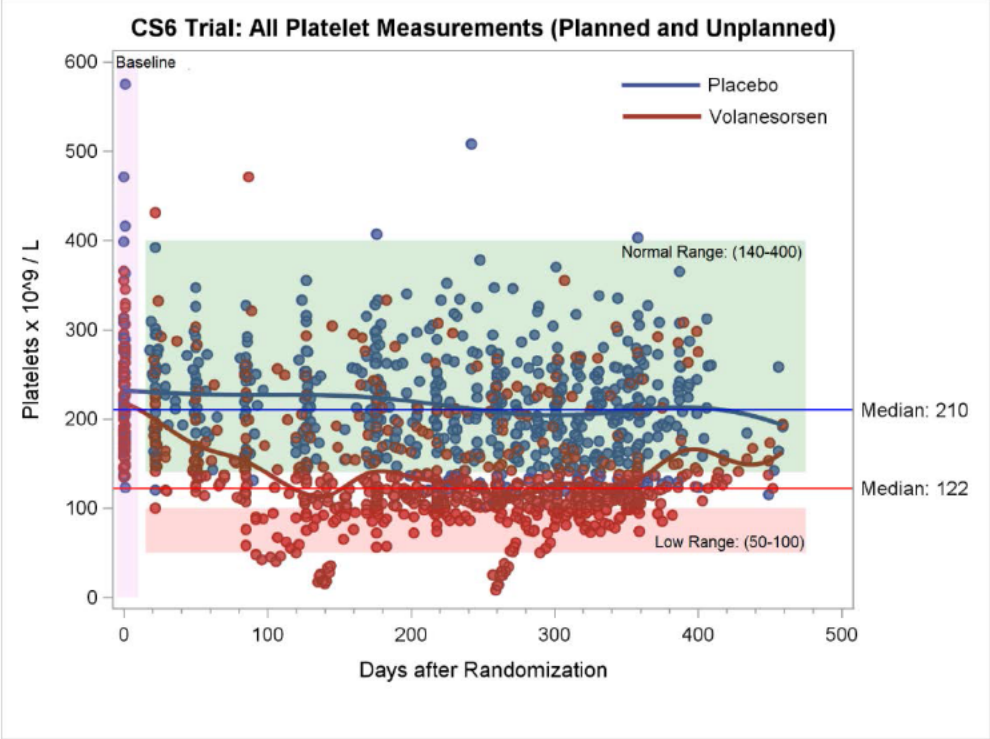
Many ASOs are reported to induce common type thrombocytopenia. The platelet count decline is gradual, mild, reversible, and dose dependent, resulting in no bleeding or only mild bleeding that may or may not require clinical intervention. However, a few cases of severe thrombocytopenia (2-5%) accompanied with moderate bleeding requiring clinical intervention were reported in some trials (Limmroth 2014, Drisapersen AC briefing, 2015, Powers 2016).

The rare type thrombocytopenia induced by ASOs has been recently reported. The thrombocytopenia of this type develops rapidly, is typically severe, may or may not be reversible, and is dose independent. Imetelstat trials reported more than 30% grade 3/4 thrombocytopenia events (CTCAE v4: thrombocytopenia Grade 3 is platelet count < 50 x 10^9/L, Grade 4 is platelet count < 25 x 10^9/L). One trial for patients with thrombocythemia, essential thrombocythemia, and myelofibrosis reported 45% grade 3/4 thrombocytopenia. Among these cases, two were irreversible and one was complicated with fatal intracranial bleeding. In addition, persistent thrombocytopenia was reported in two cases (Tefferi 2015a). Another trial in children with recurrent CNS tumors reported 30% grade 3/4 thrombocytopenia events, of which two cases of fatal intratumoral hemorrhage occurred secondary to thrombocytopenia. (Salloum 2016).

Literature describes previously unrecognized aspects of abnormal platelet biology as part of the natural history of subjects with FCS. A five-year follow up in patients with FCS who have significant hypertriglyceridemia demonstrated there is inherent platelet count instability among these patients, with unusually wide fluctuations in platelet counts in individual subjects compared to normal populations. In their study, over half (55%) of FCS subjects exhibited thrombocytopenia on one or more occasions when followed over prolonged periods of time, including up to 17% of subjects with thrombocytopenia exhibiting platelet counts <100 x 10^9/L(Gaudet 2016 and 2017).

The results of the randomized placebo controlled CS6 trial in patients with FCS demonstrated that platelet counts declined from baseline in volanesorsen recipients comparing to the placebo recipients, irrespective of the thrombocytopenia criteria or history of thrombocytopenia prior to entering the trial, as shown in Figure 1.

Figure 1: CS6 Trial Platelet counts in volanesorsen and Placebo arms



Source: Dr. Andraca-Carrera supplemental graph

Volanesorsen-induced thrombocytopenia was also observed in trials CS16 and 7, as shown in Table 3. Fewer and less severe thrombocytopenia events were observed in the CS16 trial possibly due to the shorter treatment design and the mixed patient population (seven patients with FCS were randomized in CS16; five received volanesorsen). The extension trial CS7 is still ongoing to evaluate safety and efficacy profiles of longer volanesorsen exposure in more patients with FCS. At the time of the 120-day safety updates data cut off, 23 patients in the CS7 trial had been exposed to volanesorsen for one year or more, and 5 patients had over 2 years of exposure. Of note, a few patients have received over 100 doses of volanesorsen.

Table 3: Thrombocytopenia incidence in volanesorsen Trials CS6, CS-16, and CS7[1]

Trial ID	CS6		CS16		CS7
Median cumulative doses (range)	41 (5, 53)		19 (1, 26)		25 (1, 83)
Treatment arm	Placebo	Volanesorsen	Placebo	Volanesorsen	Volanesorsen
Study patients, n (%)	33 (100)	33 (100)	38 (100)	75 (100)	60 (100)
Any Platelet count <LLN[2], n (%)	9 (27)	25 (76)	6 (16)	30 (40)	42 (70)
<LLN, but ≥ 75 x10^9/L, n (%)	9 (27)	13 (39)	6 (16)	27 (36)	36 (60)
<75x10^9/L, but ≥ 50 x10^9/L, n (%)	0	9 (27)	0	2 (3)	3 (75
<50 x10^9/L, but ≥ 25 x10^9/L, n (%)	0	1 (3)	0	1 (1)	2 (3)
<25 x10^9/L, n (%)	0	2 (6)	0	0	2 (3)

1. The data cut-off date for CS-6 and CS16 trials was 1/24/2017. The data cut-off date for CS7 trial was 8/31/2017.
2. The applicant chose 140 x10^9/L as LLN instead of the generally accepted LLN of 150 x10^9/L.

3. Volanesorsen treatment naïve patient.

Source: NDA 210645, response to IR submitted 18 Dec 2017.

Thrombocytopenia events observed in trials CS6, CS7 and CS16 were mostly gradual onset and dose dependent. In the CS6 trial, the median dose exposure was 41 doses, with only two patients receiving 53 doses and the maximal treatment duration was 372 days (Table 3). The profile of thrombocytopenia events observed in clinical trials are limited by the duration and treatment duration of exposure to volanesorsen, therefore, the limited available data is inadequate to predict long term or lifelong use of volanesorsen in patients with FCS.

Because intermittent low platelet counts have been observed in the natural history study in patients with FCS, the relative risk of thrombocytopenia was estimated using the data from the CS6 trial (Table 4). The relative risk of thrombocytopenia in patients with FCS with a median exposure of 41 doses volanesorsen vs. placebo is significantly increased 2.8-fold.

Table 4: Relative risk of thrombocytopenia with volanesorsen exposure in Trial CS6

Thrombocytopenia	Yes	No
Volanesorsen	25	8
Placebo	9	24
Relative Risk (95% CI)	Relative risk 2.8 (1.5, 5.0)	
NNT (Harm, 95%CI)	NNT 2.1 (1.4, 3.6)	

Source: Reviewer's exploratory analyses on data of NDA 210645.

Overall, no serious bleeding events were observed in volanesorsen trials, however, analysis of the CS6 trial indicated the relative risk of bleeding increased 4-fold for patients with FCS in the volanesorsen arm compared to the placebo arm (Table 5). In addition, the bleeding events excluding unrelated to injection site or lab related events was increased 6-fold for patients with FCS in the volanesorsen arm compared to the placebo arm.

Table 5: Relative risk of bleeding events in trial CS6.

Trial CS6	Number of patients with bleeding events	
Terms	Volanesorsen, N = 33 (%)	Placebo, N=33 (%)
Hemorrhage SMQ	16 (49%)	4 (12%)
RR	4.0 (95% CI 1.5, 10.7)	
NNT (Harm)	2.8 (95% CI 1.8, 6.3)	
Hemorrhage SMQ, excluding injection site-related events & lab-related events	12 (36%)	2 (6%)
RR	6.0 (95% CI 1.5, 24.8)	
NNT (Harm)	3.3 (95% CI 2.1, 8.3)	
Epistaxis	5 (15%)	0
Petechiae	4 (12%)	0

Source: Reviewer's exploratory analyses on data of NDA 210645.

The most concerning safety signal from the volanesorsen trials has been the severe thrombocytopenia defined by platelet nadir < 50 x 10^9/L. As shown in Table 6, the absolute risk of thrombocytopenia of volanesorsen-treated patients with FCS is 10%. Similarly, after pooling severe thrombocytopenia cases from three key trials, the overall incidence of severe thrombocytopenia in proposed FCS patient population is approximately 9%.

Table 6: The thrombocytopenia incidence

Study ID	FCS (n)	Severe Thrombocytopenia Case	Risk (%)
CS6	33	3	9
CS16	5	0	0
CS7	43	4	9
CS2 CFS	3	1	10
CS6 + CS7 + CS16 + CS2	84	8	10

Source: Reviewer's analyses on data of NDA 210645.

III. Mechanism Investigation for Volanesorsen Induced Thrombocytopenia

The applicant provided reports of various investigations of mechanisms for volanesorsen-induced thrombocytopenia were summarized in Table 8. The applicant's results are insufficient to reveal possible underlying mechanisms for volanesorsen-induced thrombocytopenia due to study flaws, including inadequate testing sample sizes, baseline imbalances, no real-time sampling, and limited or no human samples tested.

Table 8: Summary of mechanism investigations of volanesorsen induced thrombocytopenia

Study (trial ID)	The Applicant's Results			Reviewer Assessments
Antibody investigations				
Drug independent antiplatelet antibodies[1]	Arm	Baseline	Treated	Imbalance noted at baseline. Treatment emergent positivity doubled in both cohorts.
	VLN (24)	12.5%	25%	
	Placebo (17)	5.9%	11.8%	
Drug dependent antiplatelet antibodies	Negative in 24 patients on VLN and 17 patients on placebo			Tested in 22% (41/190) of patients exposed to volanesorsen[2].
IgG anti-PF4 antibodies	Negative in 24 patients on VLN and 17 patients on placebo			Tested in 22% (41/190) of patients exposed to volanesorsen[2].
IgM anti-PF4 antibodies[1]	Positive in 4 patients on VLN (3 with grade 4 thrombocytopenia) and 1 on placebo.			Inconclusive results.
Anti-volanesorsen and other drug antibodies (ADA)	90% of subject received VLN in CS6 trial tested positive for ADA. No known association between ADA and thrombocytopenia			Clinical pharmacology review found no consistent effect of ADA status on platelet reduction.
Other investigations				
Cytokine levels at baseline	A panel of 66 cytokines were measured in all CS6 trial patients. Increased IL-23, MIP-1beta and SDF1, and decreased TWEAK at baseline levels correlated with lower platelet counts.			No cytokine levels measured at the time of thrombocytopenia. Patients studies had dissimilar baseline cytokine levels between the VLN and placebo groups.

Study (trial ID)	The Applicant's Results	Reviewer Assessments
Platelet aggregation tests (Study AS19[3])	13-week study in Cynomolgus monkeys (14 males and 14 females), no platelet abnormality reported. Platelet aggregation test was normal.	Platelet aggregation in FCS patients on VLN is unknown.
Platelet activation by volanesorsen (IS09)	Platelet activation markers were unchanged after exposed to volanesorsen. The platelet activation increased in presence of chylomicrons.	No baseline or at the time of thrombocytopenia testing in patients.
Platelet pooling	In CS6, baseline spleen volume was 508 cc in VLN group and 454 cc in placebo group. At week 52, mean change of +107 cc in VLN group and +32 cc in placebo group.	Mild increase in spleen volume (~100cc) is unlikely to be clinically significant.
Platelet Consumption by coagulopathy	No evidence of TMA, DIC, TTP, or HIT.	Limited number of patients were evaluated except for PTT, PT, INR.
Thrombotic or embolic events	No evidence.	Limited safety data base
Megakaryocyte inhibition (Studies AS02[3] and AS11)	Study AS02 was a 13-weeks study in Cynomolgus monkeys (38 males and 38 females), no decrease of platelets was found. bone marrow samples examined and no abnormality reported. Study AS11 was a 39-week study in Cynomolgus monkeys (48 males and 48 females). Thrombocytopenia and bleeding events were seen in 5 monkeys. Platelet activation test results showed no change. No coagulation abnormality was found. No megakaryocyte inhibition was concluded based on two animal studies.	The thrombocytopenia events were seen in Monkeys after 39-weeks exposure to volanesorsen but not in those after 13-weeks. In CS6, there were limited number of patients who had bone marrow evaluation. Of the 2 patients with bone marrow evaluation, results were reported to be normal.

TMA = thrombotic microangiopathy, DIC = disseminated intravascular coagulation, TTP= thrombotic thrombocytopenic purpura, HIT = a classical heparin-induced thrombocytopenia-like mechanism, VLN = volanesorsen.

1. Four patients were positive for both anti-PF4 IgM and drug-independent anti-platelet GPIIb/IIa. Their platelet nadirs were, 8, 15, 50 and 88 x 10^9/L.
2. Of the 41 patients selected for antibodies investigation, 70% (29/41) of them has a diagnosis of FCS.
3. Exposure duration of 13 weeks in studies AS02 and AS19 were 1/3 of AS11 study treatment duration. The exposure duration of AS02 and AS11 may be insufficient to affect platelets.

Source: The reviewer's summary based on NDA 210645 volanesorsen

IV. Concomitant Use of Antiplatelet Agents and/or Anticoagulants with Volanesorsen Treatment

Aspirin (ASA) was the only concomitant agent of interest reported in trial CS6 patients. The DHP reviewer conducted an exploratory analysis in trial CS6 patients on the relative risk of bleeding events with concomitant use of ASA. The analysis result suggested that patients taking both volanesorsen and ASA had a near 2-fold increase of risk for bleeding than those taking ASA and placebo, with no statistical significance (Table 10).

Table 10: ASA and volanesorsen concomitant use and bleeding events

Concomitant Medication	Volanesorsen (n=33, %)	Placebo (n=33, %)
Patient with bleeding, N (%)	15 (45)	2 (6)
Patient received concomitant ASA	10 (33)	9 (27)
Patient with bleeding and concomitant ASA	5/10 (50)	2/9 (22)
RR (95% CI)	1.8 (0.4, 7.8)	

Source: Reviewer's exploratory analysis on data of NDA 210645, volanesorsen

No other concomitant antiplatelet or anticoagulants reported in the randomized CS6 trial for FCS patients, except only one patient with clopidogrel randomized to the volanesorsen arm. However, this patient has not received any volanesorsen or experienced any adverse event in CS6 trial at the data cut-off date (4/28/2017).

Patients who require concomitant antiplatelet or anticoagulant therapy should be assessed whether benefits of volanesorsen treatment outweigh the risks of bleeding.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	April 12, 2018
To:	Members of the Endocrinologic and Metabolic Drugs Advisory Committee
From:	Division of Risk Management (DRISK) Office of Medication Error Prevention and Risk Management (OMEPRM) Office of Surveillance and Epidemiology (OSE)
Drug Name:	Waylivra (volanesorsen) solution for injection
Application Number:	NDA 210645
Subject:	Risk Evaluation and Mitigation Strategy (REMS)

I. INTRODUCTION

This memorandum presents FDA's proposed risk evaluation and mitigation strategy (REMS) to minimize the potential risk of serious bleeding due to severe thrombocytopenia associated with volanesorsen.

II. BACKGROUND

Brief Summary of Volanesorsen

Volanesorsen is an antisense oligonucleotide that inhibits the protein synthesis of apolipoprotein C-III (apoC-III). ApoC-III inhibits lipoprotein lipase (LPL) and triglyceride-rich lipoprotein (TRL) uptake by hepatic lipoprotein receptors. Through its inhibition of apoC-III, treatment with volanesorsen results in the reduction of chylomicrons and triglycerides.

The applicant is seeking approval of volanesorsen as an adjunct to diet for the treatment of patients with familial chylomicronemia syndrome (FCS). The proposed dosing regimen of volanesorsen is 300 mg subcutaneously once weekly by self-injection.

FCS affects approximately 300-600 people in the U.S. (3,000 to 5,000 globally). FCS is an autosomal recessive genetic disorder characterized by a buildup of chylomicrons in the blood and thus severe hypertriglyceridemia. People with FCS may experience severe abdominal pain, recurrent pancreatitis, eruptive xanthomas, lipemia retinalis, hepatosplenomegaly, arthralgias and neurologic changes.

The evaluation of the efficacy and safety of volanesorsen included study CS6, the pivotal phase 3, randomized, double-blind, placebo-controlled study that included 66 patients (33 patients received volanesorsen) with FCS. Two additional studies supplemented the safety data. Study CS7 is a phase 3 open-label extension (OLE) study in 60 patients with FCS (43 patients were treatment naïve). Study CS16 is a phase 3 randomized, double-blind, placebo-controlled study in 113 patients with hypertriglyceridemia (75 patients received volanesorsen). Seven patients enrolled in study CS16 had FCS (5 received volanesorsen). Volanesorsen's clinical development program demonstrated statistically significant decreases in triglycerides in the FCS population compared to placebo.

Volanesorsen-associated Thrombocytopenia

The serious safety concern that requires consideration of a REMS to ensure the benefits outweigh the risk is a decrease in platelets and the risk of serious bleeding due to severe thrombocytopenia. In the pivotal trial, a decline in mean platelet count of approximately 30% occurred over 6 months in patients treated with volanesorsen. As of

the 120-day safety update, confirmed nadir platelet counts less than 140,000 mm^3 were observed in 25 (76%) of volanesorsen-treated patients compared to 9 (27%) patients receiving placebo; nadir platelet counts less than 100,000 mm^3 were observed in 18 (55%) in volanesorsen-treated patients and none receiving placebo; nadir platelet counts less than 25,000 mm^3 were observed in 2 (6%) in volanesorsen-treated patients and none receiving placebo. In Study CS7, nadir platelet counts less than 50,000 mm^3 were observed in 3 patients and 1 patient experienced a nadir platelet count less 25,000 mm^3. No serious bleeds or deaths due to serious bleeds occurred in these studies.

Table 1:[1] Number (%) of Patients with Nadir Platelet Counts Meeting Threshold Value at any Time Post-Baseline (Phase 3 Trial)

	Study CS6-pivotal		Study CS16-HTG		Study CS7-OLE
Nadir platelet count post-baseline	Placebo N = 33 N (%)	VLN N = 33 N (%)	Placebo N = 38 N (%)	VLN N = 75 N (%)	VLN Treatment-naïve N = 43 N (%)
100,000 to < 140,000/mm^3	9 (27)	7 (21)	5 (13)	21 (28)	11 (26)
75,000 to < 100,000/mm^3	0	6 (18)	1 (3)	6 (8)	16 (37)
50,000 to < 75,000/mm^3	0	9 (27)	0	2 (3)	3 (7)
25,000 to < 50,000/mm^3	0	1 (3)	0	1 (1)	2 (5)
< 25,000/mm^3	0	2 (6)	0	0	1 (2)
VLN = volanesorsen; HTG = hypertriglyceridemia					

Research suggests that there are two types of antisense oligonucleotide-induced thrombocytopenia that may occur, a common and a rare form. The common form is characterized by a gradual decline in platelets, which is usually mild, transient and dose-dependent with patients presenting as asymptomatic or with mild to moderate bleeding.[2] The rare form is characterized by a rapid and severe decrease in platelets accompanied by severe and potentially fatal bleeding. Platelet counts can be normalized after discontinuation but thrombocytopenia recurs with drug rechallenge. The type of thrombocytopenia that occurs in patients treated with volanesorsen is unknown.

In most patients that experienced a decrease in platelets associated with volanesorsen, the platelet count recovered when treatment was paused or discontinued. In severe cases of thrombocytopenia, steroids and immunoglobulin (IVIG) were administered to treat the decrease in platelets. The impact of long-term exposure to volanesorsen on

[1] Roberts M. Division of Metabolism and Endocrinology Products. Volanesorsen (Waylivra). Endocrinologic and Metabolic Drugs Advisory Committee Meeting Executive Summary (draft). March 14, 2018.

[2] Chi X, Gatti P, Papoian T. Safety of antisense oligonucleotide and siRNA-based therapeutics. Drug discovery today. 2017;22(5):823-833.

platelets is unknown. It's also unknown as to whether patients with FCS have inherent platelet dysfunction which could contribute to the volanesorsen-associated thrombocytopenia.

Platelet monitoring in the pivotal trial, Study CS6, was intensified after 2 patients with severe thrombocytopenia (platelets < 25,000 mm^3) were identified (including 1 patient on weekly monitoring). A, "Notice of Implementation of Early Safety Measures" modified the routine platelet monitoring to every 2 weeks. Weekly monitoring was instituted for platelets 140,000 mm^3 to 75,000 mm^3 and platelet counts less than 75,000 mm^3 were monitored every 2-3 days. As described in the FDA clinical review, a patient can have a normal platelet count (> 140,000 mm^3) and experience a severe drop before the next routine platelet count is obtained.

Risk Evaluation and Mitigation Strategy

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007 (FDAAA) authorizes the FDA to require pharmaceutical sponsors to develop and comply with a REMS for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert (PPI), a communication plan to healthcare providers, elements to assure safe use, and an implementation system. FDAAA also requires that all REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) have a timetable for submission of assessments of the REMS. These assessments are prepared by the sponsor and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient's decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA approved materials used to aid a sponsor's implementation of the REMS and/or inform healthcare providers about serious risk(s) of an approved product. This can include, for example, "Dear Healthcare Professional" letters, collaboration with professional societies, and education pieces (such as letters,

drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry

Because ETASU can impose significant burdens on the healthcare system and reduce patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

III. RISK MANAGEMENT CONSIDERATIONS

A variety of strategies are used to minimize risks associated with drugs and therapeutic biologics. These strategies can minimize risks in several ways. They can communicate specific risk information, as well as information regarding optimal product use. In addition, they can provide guidance and encourage, remind, or support adherence to certain prescribing, dispensing, or monitoring requirements, and/or limit use of a product to only the most appropriate patients where the benefits outweigh the risks.

Because of the potential risk of serious bleeding due to severe thrombocytopenia, volanesorsen cannot be approved without the necessary safeguards to restrict prescribing to certified prescribers. They should be educated about the risk of serious bleeding due to severe thrombocytopenia and understand the need to closely monitor patients who receive volanesorsen. Prescribers should also understand the need to

counsel patients about the risk of thrombocytopenia, the importance of adhering to the laboratory monitoring schedule, the early symptoms of bleeding, and when to seek medical attention.

Proposed REMS Strategy

FDA is proposing that the REMS have the following goals:

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

1. Ensuring that healthcare prescribers are educated on the following:
    a. Severe thrombocytopenia associated with volanesorsen that could lead to serious bleeding
    b. Monitoring recommendations and treatment modifications when there is a decline in platelets per the prescribing information
    c. The need to counsel patients about the risk of severe thrombocytopenia, the importance of adhering to the laboratory monitoring schedule, the early symptoms of bleeding, and when to seek medical attention.
2. Ensuring that patients are informed about:
    a. The risk of severe thrombocytopenia, the signs and symptoms of bleeding and when to seek medical attention
    b. The need to routinely monitor platelets
3. Enrollment of all patients in a registry to further support long-term safety and safe use of volanesorsen

FDA proposes the following components for the REMS.

1. Elements to assure safe use including:
    - Healthcare providers who prescribe volanesorsen must be specially certified
    - Pharmacies who dispense volanesorsen must be specially certified
    - Volanesorsen must be dispensed to patients with documentation of safe-use conditions which may include a patient-prescriber agreement form at the time treatment is initiated
    - Each patient using volanesorsen is subject to specific monitoring that is documented via a patient status form and submitted to the REMS program by the prescriber every 90 days
    - Each patient using volanesorsen must be enrolled in the REMS registry to further support long-term safety and safe use of volanesorsen
2. An implementation system
3. A timetable for submission of assessments

Healthcare providers who prescribe volanesorsen must be specially certified

The FCS patient population is typically managed by endocrinologists and lipidologists. Requiring prescriber certification will ensure that prescribers are: educated and enrolled in the volanesorsen REMS program; acknowledge they are aware of the risk of serious bleeding due to severe thrombocytopenia; understand the need to monitor platelets during treatment; and understand the need to modify treatment when there is a decline in platelets as per the prescribing information. Prescribers would also be required to enroll patients in the REMS program and counsel patients about the risk of serious bleeding due to severe thrombocytopenia, the importance of adhering to the laboratory monitoring schedule, the early symptoms of bleeding, and when to seek medical attention.

Volanesorsen must be dispensed to patients with documentation of safe-use conditions

FDA proposes the following safe use conditions: Prescribers and patients would be required to complete and sign a patient-prescriber agreement form (PPAF) as part of the REMS enrollment. The PPAF is completed once at the time of treatment initiation. The PPAF would serve as a counseling tool for the prescriber and document that patient was informed of the risks of volanesorsen, the need for routine monitoring, the symptoms of bleeding, and when the patient should seek medical attention. The PPAF is also used to enroll the patient in the REMS registry to further support long-term safety and safe use of volanesorsen.

Each patient using volanesorsen is subject to specific monitoring

Each patient using volanesorsen is subject to specific monitoring at regular intervals. The prescriber would be required to complete a patient status form for each patient. The form could collect information about; serious bleeds, significant declines in the patient's platelet count, whether volanesorsen treatment needed to be modified or discontinued due to a decline in platelets, and the frequency that the platelet counts were monitored. The FDA is proposing that the prescribers complete the patient status form every 90 days.

Pharmacies who dispense volanesorsen must be specially certified

Pharmacies would need to be certified to ensure that systems are in place to verify that volanesorsen is only dispensed to patients who are enrolled and have a prescription written by a prescriber certified in the REMS program. The certified pharmacies would also need to confirm that the patient status form was completed within the past 90 days prior to dispensing volanesorsen. The proposed REMS program would not require documentation about the patient's medical need for volanesorsen. Pharmacies would

not be required to ensure that the appropriate laboratory testing has been performed prior to dispensing volanesorsen.

Discussion of the Proposed Strategy

In considering risk management strategies for volanesorsen the benefit of treatment must be weighed carefully against potential risk of serious bleeding due to severe thrombocytopenia. As detailed prior, the proposed elements of the REMS provide greater assurance that prescribers are educated about the risks and the need to carefully monitor patients for a decline in platelet counts, thrombocytopenia and bleeding. Enrolling patients in the REMS will provide greater assurance that they are aware of the risk and the need for frequent monitoring and the registry will further support long-term safety and safe use of volanesorsen.

The REMS is designed to prevent or attenuate the risk of serious bleeding due to severe thrombocytopenia if the decline in platelets is gradual and patients are monitored per the labeled recommendations. However, a rapid and severe decrease in platelets may not be detected even with rigorous monitoring. This was demonstrated in the pivotal study which highlights, despite strict monitoring, severe thrombocytopenia may not be prevented. Therefore, requiring every 2-week monitoring as part of the REMS may not detect a rapid fall in platelets. Rather, the REMS will ensure that prescribers and patients are educated about the signs and symptoms of bleeding that are associated with severe thrombocytopenia.

It is important to note that if approved, the proposed REMS ability to mitigate serious bleeding due to severe thrombocytopenia will be impacted by the rate of the platelet decline as well as prescriber and patient adherence to labeled monitoring recommendations and treatment modifications when there is a decline in platelets.

IV. CONCLUSION

FDA has the authority to require a REMS if additional measures beyond the approved labeling are necessary to ensure the benefits of a drug outweigh the risks. In considering a risk management approach for volanesorsen, FDA may consider that the FCS patient population currently has limited therapeutic options. On the other hand, the risk-benefit profile of volanesorsen has not been established and is the topic of this advisory committee. The committee will be asked to discuss whether a REMS is necessary and if it would be able to ensure that the benefits of volanesorsen outweigh the potential risk of serious bleeding due to severe thrombocytopenia. The committee will also be asked to discuss whether the FDA's proposed REMS is adequate or whether changes are recommended.

Pharmacology and Toxicology Summary
Daniel R Minck, PhD

Background

Volanesorsen is a single-stranded antisense oligonucleotide (ASO) targeted to human apoC-III. The ASO is comprised of nucleotides that have been modified with phosphorothioate (PS) substitutions and includes five 2′-*O*-methoxyethyl (2'-MOE) modified ribonucleosides at both the 5'and 3' ends of the structure. The modifications improve the binding affinity for the targeted mRNA and protect against exonuclease-mediated degradation. Volanesorsen is considered to be a 2nd generation PS ASO.

Mechanism of Action

Volanesorsen targets ApoC-III mRNA. Binding of volanesorsen to the target mRNA results in ribonuclease H1 (RNase H1)-mediated degradation of the ApoC-III mRNA. By reducing the amount of ApoC-III, plasma triglyceride levels are lowered.

ApoC-III is a protein that is primarily synthesized in the liver and has a significant role in regulating plasma triglyceride (TG) levels. ApoC-III inhibits lipoprotein lipase (LPL)-catalyzed hydrolysis of TG-rich lipoproteins while increased ApoC-III content adversely affects apolipoprotein E (ApoE)-mediated hepatic uptake of triglyceride rich lipoproteins. ApoC-III also inhibits hepatic lipase activity, an enzyme involved in the conversion of very low density lipoprotein (VLDL) to intermediate and low-density lipoproteins. High levels of ApoC-III results in reduced clearance of triglyceride-rich lipoproteins from plasma resulting in hypertriglyceridemia. There is also evidence that ApoC-III may be atherogenic.

Nonclinical Program

The nonclinical pharmacology program evaluated the ability of volanesorsen to reduce hepatic apoC-III mRNA levels, apoC-III protein levels in plasma, and/or TG levels in both in vitro and in vivo studies. The in vitro pharmacological activity was characterized in a human hepatoma cell line (HepG2) and in primary hepatocytes from human, cynomolgus monkeys, and *APOC3* transgenic mice. These studies demonstrated concentration-dependent reductions in apoC-III mRNA levels. In the in vivo studies, volanesorsen (and species specific versions of it) was found to reduce apoC-III mRNA and protein levels, as well as TG levels in various models, including transgenic mice expressing the human APOC-III transgene and in animal models of hypertriglyceridemia. A murine version was also shown to lead to reductions in atherosclerotic lesion area and volume in mice expressing the human cholesterol ester transfer protein (CETP) transgene. Safety pharmacology studies evaluating neurobehavioral, pulmonary, and cardiovascular function revealed no significant effects.

The toxicology program was primarily conducted in mice and monkeys, with some studies conducted in the rat. In some rodent studies, a species-specific version of the apoC-III ASO was included to evaluate the effects related to the pharmacologic activity of the compound. The monkey is considered the most representative species for human safety assessment based on volanesorsen being homologous with monkey RNA and its sensitivity to some of the nonspecific 2′-MOE ASO class effects, such as the inflammatory effects and accumulation of oligonucleotide in target tissues. Across species and studies, the primary drug-related effects were noted in the kidney and liver, which are the principal organs responsible for the uptake and distribution of volanesorsen. Notable effects were also evident in the heart in rodents, which were related to the inflammatory effects of the drug. Reductions in platelet counts were seen in mice and monkeys, with the effects in monkeys being significant. There was no toxicity identified that was specifically associated with a reduction in apoC-III expression (via the use of species-specific surrogates).

The pivotal nonclinical toxicology studies with notable findings and exposure margins at the no observed adverse effect level (NOAEL) and lowest observed adverse effect levels (LOAEL) identified in each study are summarized below in . Observations related to the uptake of the ASO (eg, accumulation of basophilic granules into various tissues, vacuolated/granular macrophages, mononuclear cell infiltration, etc) are not included as these observations did not drive the determination of the study NOAELs.

Of the observed effects in the nonclinical toxicology studies, those described below are noteworthy from the Pharmacology/Toxicology perspective:

- Reduced platelet counts were seen in multiple species. In monkeys, the reductions in platelet counts were associated with clinical signs of bleeding, consistent with thrombocytopenia. Multiple animals were given dosing holidays but were subsequently terminated early either due to lack of recovery following cessation of treatment or a decline in platelet counts once treatment was re-initiated.
- Accumulation of drug in the kidney resulted in tubular vacuolation in multiple species. Associated effects included changes in multiple urine chemistries/proteinuria endpoints suggestive of impaired renal function.
- Evidence of inflammation consisting of increased cytokine/chemokine levels, complement activation, and microscopic effects were observed in multiple species. In rodents, inflammation of the heart was associated with myofiber degeneration and fibrosis. However, rodents are more sensitive to the pro-inflammatory effects of ASOs than monkeys.
- Increases in tumors at the injection site in rats were considered related to the treatment procedure and are unlikely to be of clinical concern. In mice, the hemangiosarcomas, histiocytic sarcomas, and hepatocellular adenomas likely reflect the increased sensitivity of mice to the pro-inflammatory effects of the test article

while the increase in pituitary adenomas are likely related to the high background rate of pituitary hyperplasia in this species.

Table 1: Non-Clinical Summary Table & Safety Margins

Study and Observations	NOAEL[a] (No Observed Adverse Effect Level)	Safety Margin*
Chronic (26-week) Mouse Study (0, 3, 10, 30, 80 mg/kg/wk)		
• Adverse effects at 80 mg/kg/wk, equivalent to clinical exposure levels (1.3x*): – Heart - multifocal myofiber degeneration, fibrosis, and multifocal histiocytic infiltrate at 80 mg/kg/wk (3.4x[b] / 1.3x) leading to death/early termination – Kidney - ↑ urea nitrogen, ↓ albumin, altered electrolytes suggestive of impaired functioning at 80 mg/kg/wk • Adverse effects at ≥30 mg/kg/wk, ½ of clinical exposure levels (0.5x*): – Liver - ↑ increased ALT/AST and Kupffer cell hypertrophy – 50% decrease in platelets • Effects still evident after the treatment-free period at 80 mg/kg/wk, but had reversed at 10 mg/kg/wk (no recovery data collected at 30 mg/kg/wk): – Immune effects including ↑ spleen weights at ≥30 mg/kg/wk – ↑ Cytokines at 80 mg/kg/wk	10 mg/kg/wk	0.2x
Chronic (26-week) Rat Study (0, 3, 10, 40/20, 80 mg/kg/wk)		
• Mortality of 1 animal at 80 mg/kg/wk (3-fold higher than clinical exposure levels, based on BSA), associated with signs of a systemic immune response and nephropathy. • Adverse effects at ≧40/20 mg/kg/wk, equivalent to clinical exposure levels (0.7x*): – Heart - thickening of valve leaflets – Kidney - ↑ urinary protein, protein/creatinine ratio, albumin and/or albumin/creatinine ratio, tubular vacuolation, and ↑ severity of chronic progressive nephropathy (↑ incidence at 10 mg/kg/wk also) • Non-adverse systemic inflammatory responses at ≥10 mg/kg/wk: – ↑ Spleen weights, lymphoid hyperplasia in spleen, lymphohistiocytic cell infiltrates in kidney, inflammatory cell infiltrates – ↑ Cytokines/chemokines	♂: 3 mg/kg/wk ♀: 10 mg/kg/wk	♂: 0.1x ♀: 0.3x
Chronic (39-week) Monkey Study (3, 6, 12, 20 mg/kg/wk)		
➢ ***Thrombocytopenia***-related mortalities associated with petechia, bruising, and decreases in platelets at ≥12 mg/kg/wk, approximately equivalent to clinical exposure levels (0.8x*). • Systemic inflammatory responses at ≧12 mg/kg/wk (at clinical exposures) – Mononuclear cell infiltrates in multiple tissues – ↑ Bb and ↓ C3 levels – ↑ Cytokine levels • Kidney toxicity at ≧12 mg/kg/wk (at clinical exposures) – ↑ Urinary protein/creatinine ratio and tubular vacuolation	6 mg/kg/wk	0.4x

– Microscopic changes reflecting an immune response (increased macrophage activation, histiocytosis, and Kupffer cell enlargement) • Liver toxicity at ≥12 mg/kg/wk (at clinical exposures) – Microscopic changes reflecting an immune response (increased macrophage activation, histiocytosis, and Kupffer cell enlargement) – ↑ Mixed cell infiltrates at 20 mg/kg/wk			
Carcinogenicity Mouse Study (6, 25, 40 mg/kg/wk)			
Statistically significant Increases in incidences of drug-related neoplasms were observed at ≥6 mg/kg/wk, below clinical exposure levels based on BSA. – Hepatocellular adenomas in males – Multicentric hemangiosarcomas in males – Multicentric histiocytic sarcomas in females – Pituitary gland adenomas in females		<6 mg/kg/wk	<0.1x
Carcinogenicity Rat Study (0.2, 1, 5 mg/kg/wk)			
Statistically significant Increases in incidences of drug-related neoplasms were observed at ≥1 mg/kg/wk, below clinical exposure levels based on BSA. – Malignant fibrous histiocytomas in the skin/subcutis of injection sites in males and females		0.2 mg/kg/wk	0.006x
Fertility and Embryofetal Development			
No adverse effects at the highest dose tested	mouse	>87.5 mg/kg/wk	>1.4x
Embryofetal Development			
Abortions at 52.5 mg/kg/wk, 3-fold higher than clinical exposure levels based on BSA	rabbit	21 mg/kg/wk	1.4x
Pre- and Postnatal Development			
Reduced weights of suckling pups were associated with delays in developmental milestones at doses of 87.5 mg/kg/wk (1.4-fold clinical exposure levels, based on BSA) administered to pregnant and lactating dams	mouse	35.5 mg/kg/wk	0.6x
* Based on Body Surface Area (BSA) relative to a once weekly clinical dose of 300 mg in a 60 kg human. a - No Observed Adverse Effect Level (NOAEL)			