# EU Risk Management Plan For WAYLIVRA® (Volanesorsen)

## RMP version to be assessed as part of this application:

| | |
|---|---|
| RMP Version number | 3.0 |
| Data lock point for this RMP | 25 Oct 2024 |
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| Rationale for submitting an updated RMP | RMP was updated to version 3.0 to include the WAY4001 PASS timeline extension with Waylivra Type 1B C.I.11.z variation. |
| Summary of significant changes in this RMP | RMP Part III Sections, III.2 and III.3; Part V Sections, V.2 and V.3; and Annex 2 were updated to include the WAY4001 PASS timeline extension with Waylivra Type 1B C.I.11.z variation.<br><br>Dates of completion of milestones for WAY4001 PASS and registry was updated in alignment with the updated PASS protocol version 5.0 |
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| Submitted on | Not applicable |
| Procedure number | Not applicable |
| Details of the currently approved RMP: | |

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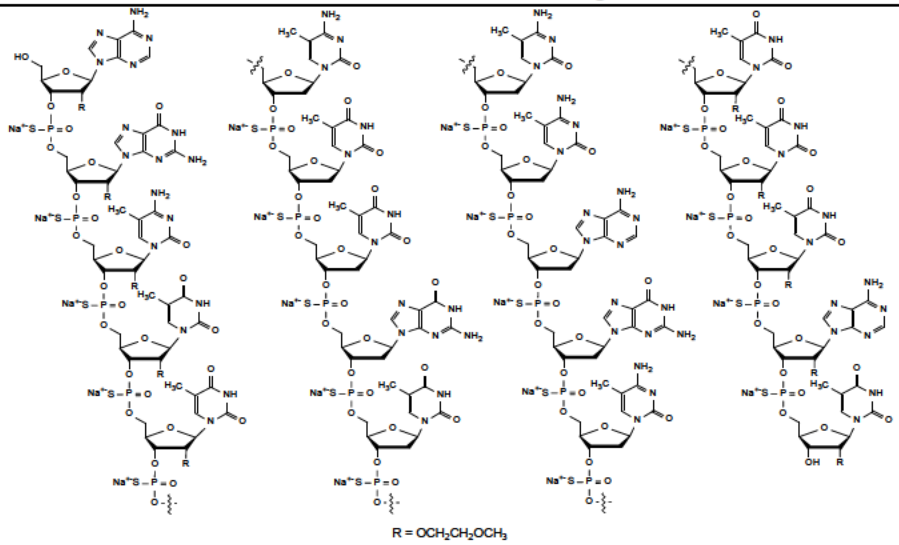
# LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| ADA | anti-drug antibodies |
| AE | adverse event |
| ALT | alanine aminotransferase |
| apoC-III | apolipoprotein C-III |
| ASO | antisense oligonucleotide |
| AST | aspartate aminotransferase |
| aRMMs | additional risk minimisation measures |
| ATU | Temporary Authorization for Use |
| CETP | cholesteryl ester transfer protein |
| CHMP | Committee for Medicinal Products for Human Use |
| EAMS | Early Access to Medicines Scheme |
| EAP | expanded access programme |
| ECG | electrocardiogram |
| EEA | European Economic Area |
| EMA | European Medicines Agency |
| EPAR | European Public Assessment Report |
| EU | European Union |
| FCS | familial chylomicronemia syndrome |
| FDA | Food and Drug administration |
| HCP | health care provider |
| HDL | High density lipoprotein |
| HTG | hypertriglyceridaemia |
| LDLR | low density lipoprotein receptor |
| LPL | lipoprotein lipase |
| MAH | Marketing Authorisation Holder |
| MOE | methoxyethyl |
| NORD | National Organisation for Rare Disorders |
| NOAEL | no-observed-adverse-effect levels |
| NSAIDs | nonsteroidal anti-inflammatory drugs |
| PASS | Post-Authorisation Safety Study |
| PK | pharmacokinetics |
| PRAC | Pharmacovigilance Risk Assessment Committee |
| PSP | patient support programme |
| RMP | risk management plan |

| Abbreviation | Definition |
|---|---|
| SAE | serious adverse event |
| SAP | special access programme |
| SHTG | severely high triglycerides |
| SmPC | Summary of Product Characteristics |
| SMQ | Standardised MedDRA Query |
| SOC | system organ class |
| T2DM | type 2 diabetes mellitus |
| TG | triglyceride |
| UK | United Kingdom |
| ULN | upper limit of normal |
| VLDL | very low-density lipoprotein |

# PART I: PRODUCT OVERVIEW

| | |
|---|---|
| **Active substance(s) (INN or common name)** | Volanesorsen (also known as ISIS 304801) |
| **Pharmacotherapeutic group(s) (ATC Code)** | Cardiovascular system, Other lipid modifying agents<br>(C10AX18) |
| **Marketing Authorisation Holder** | Akcea Therapeutics Ireland Limited |
| **Medicinal products to which this RMP refers** | One, Waylivra 285 mg solution for injection in pre-filled syringe |
| **Invented name in the European Economic Area (EEA)** | WAYLIVRA® |
| **Marketing authorisation procedure** | Centralised |
| **Brief description** | **Chemical class:**<br>Volanesorsen is a second generation 2′-*O*-(2-methoxyethyl) chimeric antisense oligonucleotide (ASO) inhibitor of the molecular target apolipoprotein (apo) C-III. |
| | **Summary of mode of action:**<br>Volanesorsen is an ASO designed to inhibit the formation of apolipoprotein C-III (apoC-III), a protein that is recognised to regulate both triglyceride metabolism and hepatic clearance of chylomicrons and other triglyceride-rich lipoproteins. The selective binding of volanesorsen to the apoC-III messenger ribonucleic acid (mRNA) within the 3′ untranslated region at base position 489-508 causes the degradation of the mRNA. This binding prevents translation of the protein apoC-III, thus removing an inhibitor of triglyceride clearance and enabling metabolism through an lipoprotein lipase (LPL)-independent pathway. |
| | **Important information about its composition:**<br>Volanesorsen is the nonadecasodium salt of a 20-base residue (20-mer) phosphorothioate oligonucleotide. Each of the 19 internucleotide linkages is a 3′-*O* to 5′-*O* phosphorothioate diester. The 5 sugar residues on the 3′ and 5′ ends are 2′-*O*-(2-methoxyethyl)-D-ribose (MOE). The 10 sugar residues in the middle are 2-deoxy-D-ribose. All of the cytosine bases are methylated at the 5-position. The volanesorsen sequence can be written in shorthand as follows:<br>5′-A$\underline{G}^{Me}\underline{C}^{Me}\underline{U}^{Me}\underline{U}^{Me}$CTTGT$^{Me}$C$^{Me}$CAG$^{Me}$C$^{Me}\underline{U}^{Me}\underline{U}^{Me}\underline{UA}^{Me}\underline{U}$-3′<br>The underlined residues are 2′-MOE nucleosides. It should be noted that 2′-*O*-(2-methoxyethyl)-5-methyluridine (2′-MOE MeU) nucleosides are sometimes referred to as 2′-*O*-(2-methoxyethyl)ribothymidine (2′-MOE T).<br>The structure of volanesorsen is shown below: |

| | |
|---|---|
| |  |
| **Hyperlink to the Product Information** | Product Information (CTD module 1.3.1) |
| **Indication(s) in the EEA** | Current:<br>WAYLIVRA is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate. |
| | Proposed: N/A |
| **Dosage in the EEA** | Current:<br>The recommended starting dose is 285 mg in 1.5 ml injected subcutaneously once weekly for 3 months. Following 3 months, dose frequency should be reduced to 285 mg every 2 weeks. After 6 months of treatment with volanesorsen, increase of dose frequency to 285 mg weekly should be considered if response has been inadequate in terms of serum triglyceride reduction as evaluated by the supervising experienced specialist and in the condition that platelet counts are in the normal range. Patients should be re-downtitrated to 285 mg every 2 weeks if the higher 285 mg once weekly dose does not provide significant additional triglyceride reduction after 9 months. |
| | Proposed: N/A |
| **Pharmaceutical form(s) and strengths** | Current:<br>Volanesorsen is formulated as a clear colourless to slightly yellow solution with a pH of approximately 8 and osmolarity of 363-485 mOsm/kg for injection. Each ml contains 200 mg volanesorsen sodium, equivalent to 190 mg volanesorsen. Each single-dose pre-filled syringe contains 285 mg of volanesorsen in 1.5 ml solution. |
| | Proposed: N/A |
| **Is the product subject to additional monitoring in the EU?** | Yes |

# PART II: MODULE SI – EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

## Indication

WAYLIVRA is indicated as an adjunct to diet in adult patients with genetically confirmed familial chylomicronemia syndrome (FCS) and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

## Incidence and Prevalence

Familial chylomicronemia syndrome is a serious, rare disorder of lipid metabolism characterised by extremely high serum triglycerides (TG) (> 750 mg/dL, 8.5 mmol/L) that are carried primarily in chylomicrons (dietary lipids) (Brahm and Hegele 2015), affecting an estimated 3000-5000 patients globally. Chylomicrons are large (~ one micron in diameter) lipoprotein particles that, if elevated, can result in clinically significant manifestations, including reduction of blood flow through the pancreatic microcirculation leading to severe abdominal pain and pancreatitis (Valdivielso et al. 2014). Risks of chylomicronemia include acute pancreatitis, which can be fatal or lead to pancreatic damage, resulting in permanent exocrine or endocrine insufficiency (Symersky et al. 2006), in addition to other symptoms and complications.

Estimated prevalence of FCS meets the regional definitions for an orphan population as defined by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) and volanesorsen has been granted orphan designation in both jurisdictions for treatment of FCS.

Based on systematic survey of the literature on rare diseases in Europe, the Orphanet Rare Disease collection (Orphanet 2016) estimates a prevalence for FCS of 1 per 1,000,000 of the European population. The prevalence may be higher in certain geographical areas with founder populations.

Nierman and coworkers report of an extensive track down of all FCS patients with lipoprotein lipase (LPL) deficiency in the Netherlands (Nierman et al. 2005). Loss-of-function mutations in the gene coding for LPL are the most common cause of FCS (Johansen and Hegele 2011). The prevalence of FCS is estimated as 2:1,000,000 for the Netherlands (Nierman et al. 2005). As LPL deficiency accounts for the majority of documented FCS cases, it is considered acceptable to use a prevalence of 2:1,000,000 as basis for the calculation of current prevalence of FCS for this country.

An estimate of the prevalence of FCS was published by the National Institute for Health Research in United Kingdom in a summary report describing a new drug in development. Prevalence is estimated as 1 in 1,000,000 individuals; however, without clearly allocating the reference population for this estimate (NIHR 2013).

In a review article on hypertriglyceridaemia, the prevalence of FCS is estimated as 1:1,000,000. The reference population for this estimate is not specified (Yuan et al. 2007).

National Organisation for Rare Disorders

In a recent summary article published by the National Organisation for Rare Disorders (NORD), a federation of voluntary health organisations in the United States, familial LPL deficiency is estimated to occur in 1 per 250,000 in the general population, in all races (NORD 2013). This

estimate is higher than the estimate given by most of the other publications on this topic, and it remains unclear what data are underlying this estimation, as a reference is not provided. Therefore, this publication is not considered for the calculation of the prevalence of FCS in the Community. A summary of the references is provided in Table 1.

**Table 1: Prevalence of Familial Chylomicronemia Syndrome**

| Region | Prevalence | Reference |
|---|---|---|
| Europe | 1:1,000,000 | (Orphanet 2016) |
| The Netherlands | 2:1,000,000 | (Nierman et al. 2005) |
| United States | 1 to 2:1,000,000 | (Gaudet et al. 2013) |
| Japan | 1 to 2:1,000,000 | (Gotoda et al. 2012) |
| Not specified | 1:1,000,000 | (Yuan et al. 2007) |
| Not specified | 1:1,000,000 | (NIHR 2013) |
| United States of America (general population) | 1 to 2:1,000,000 | (Physicians 2015) |

Like many rare diseases, FCS is likely to be under-recognised and therefore underdiagnosed. Due to the limited clinician recognition or knowledge of FCS, patients may be misdiagnosed (Gotoda et al. 2012), often seeing multiple clinicians before an accurate diagnosis is made. The prevalence of FCS in the European Economic Area is estimated as 1 in 1,000,000 individuals (Orphanet 2016).

**Demographics of the Target Population – Age, Sex, Race/Ethnic Origin**

A specific diagnosis of FCS can be made based on clinical characteristics (Brunzell 1999-2011). The hallmark of chylomicronemia is lipemic blood, caused by the presence of sustained serum chylomicrons, even in the fasting state. Per medical practice, the exclusion of identifiable secondary and environmental causes of high triglycerides is critical, but once this is done diagnosis is straightforward.

The presence of the following clinical criteria provides a specific diagnosis of FCS:

1. Fasting TG levels in excess of 8.5 mmol/L or 750 mg/dL (chylomicronemia) that are refractory to standard lipid-lowering therapy (Brahm and Hegele 2015)

   AND

2. One of the following:
   - History of acute pancreatitis OR
   - History of childhood pancreatitis OR
   - History of recurrent abdominal pain without other explainable cause OR
   - Family history of hypertriglyceridaemia
3. Exclusion of contributing factors, e.g., the persistence of chylomicronemia described above after attempts to remove exacerbating causes through diet modification, discontinuation of drugs known to increase TG levels, and/or provision of insulin therapy

for patients with poorly treated diabetes mellitus (Miller et al. 2011). In addition, the contribution of other causes of pancreatitis (e.g., alcoholism, gallstones) should also be ruled out.

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

Although there are references in the literature that state that FCS most often presents in childhood, it may be first diagnosed at any age, and shows no difference across race, gender, or ethnicity (Brunzell 1999-2011).

**Main Treatment Options**

Currently, there is no approved therapeutic agent specifically indicated for the treatment of FCS other than WAYLIVRA. Standard therapeutic TG lowering agents such as fibrates, fish oils, and niacin are largely ineffective in this population, as is the use of statins (Brahm and Hegele 2015, Stroes et al. 2017).

The only option to manage serum TG levels in FCS patients is an extremely restrictive diet devoid of nearly all dietary fat, ideally ~10g - 20g or less daily, the equivalent of about one tablespoonful of olive oil (Brunzell 1999-2011, Valdivielso et al. 2014) and strict avoidance of alcohol and classes of drugs that are known to increase TG levels. Even short-term ingestion of dietary fat or limited alcohol consumption can result in highly exaggerated TG excursions that place the patients at high risk for acute pancreatitis, despite the fact that for the vast majority of time they may have exhibited exemplary compliance to their restricted dietary and lifestyle prescriptions. Even in patients with strict dietary adherence, TG levels may remain at dangerously high levels, demonstrating that diet alone does not sufficiently mitigate the risk of pancreatitis in all patients (Gaudet et al. 2010, Ceska et al. 2016, Stroes et al. 2017).

There are 2 therapeutic ingredients that have received orphan designation in the European Union (EU) for FCS: lomitapide (EMA/COMP/639953/2010 Rev.2) and pradigastat (EMA/COMP/527251/2012). Neither of these drugs is authorised for marketing nor in clinical development for this patient population.

Alipogene tiparvovec (Glybera 2012) is a LPL gene therapy that was granted orphan designation in the EU and received approval under exceptional circumstances from the EMA for the treatment of homozygous LPL deficiency in 2013 and, according to the Summary of Product Characteristics (SmPC), a subset of FCS patients would be eligible for Glybera treatment. However, the company has stated publicly that it will not seek to continue the authorisation and the marketing authorisation for alipogene tiparvovec expired on 28 October 2017.

Therefore, disease management approaches are required for patients with FCS in order to effectively prevent pancreatitis attacks and other consequences of prolonged chylomicronemia.

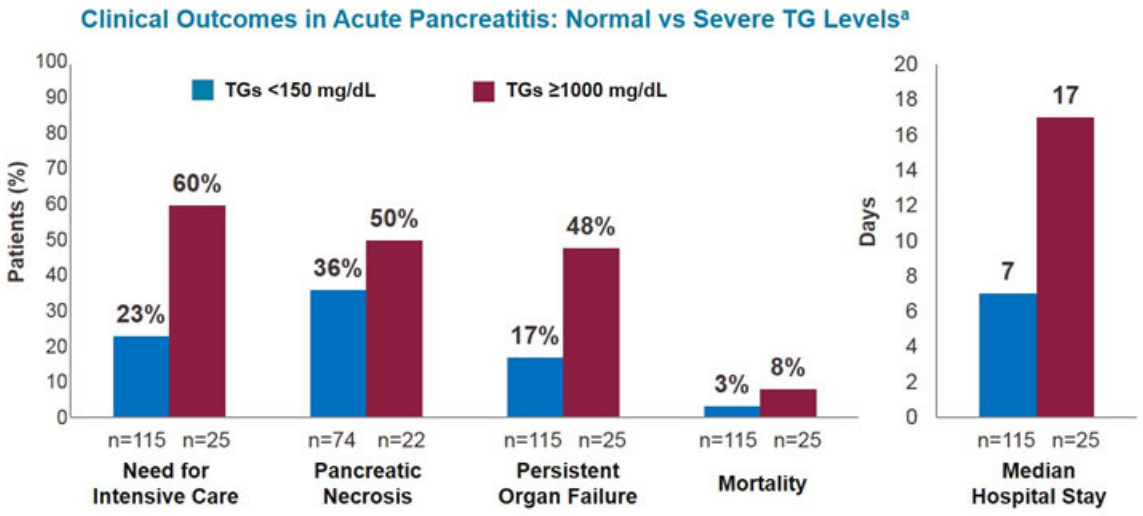
Volanesorsen sodium is a second-generation 2′-*O*-(2-methoxyethyl) chimeric antisense oligonucleotide inhibitor of the molecular target apolipoprotein C-III (apoC-III), designed to bind the human apoC-III messenger ribonucleic acid (mRNA), resulting in ribonuclease H1 (RNase H1)-mediated degradation of the apoC-III mRNA, thus inhibiting translation of the protein. Through a novel, apoC-III-lowering mechanism of action, volanesorsen has shown consistent and

dose-dependent sustained efficacy in patients studied to date, with and without concomitant lipid-lowering therapy (e.g., statins and fibrates).

**Natural history of the indicated condition in the population, including mortality and morbidity and co-morbid conditions:**

Patients with FCS have a number of severe and potentially life-threatening complications associated with the disease. Approximately 65-80% of patients with FCS will experience acute pancreatitis (Gaudet 2016). Acute pancreatitis presents the most significant clinical risk in patients with FCS, with potential mortality and other significant complications (Davidson 2017). Long-term complications may include chronic pancreatitis, pancreatogenic (type 3c) diabetes and endocrine and exocrine pancreatic insufficiencies, leading to digestive issues, steatorrhea, and diabetes (Symersky et al. 2006). The scientific literature has shown that pancreatitis due to severely high TG (SHTG) may be more severe with worse outcomes than pancreatitis of other aetiologies. In one study, compared with acute pancreatitis in patients with lower TG levels (< 150 mg/dL), the acute pancreatitis in the cohort of patients with SHTG resulted in longer median hospital stays (17d vs. 7d), increased need for intensive care (60% vs. 23%), a higher rate of pancreatic necrosis (50% vs. 36%), and more frequent persistent (i.e., > 48 hr) organ failure (48% vs. 17%) (Figure 1) (Nawaz et al. 2015). Further, persistent organ failure within the first week of severe acute pancreatitis has been associated with a higher mortality rate (Johnson and Abu-Hilal 2004). Patients with high TG and minimal LPL activity (i.e., FCS patients) may also be at enhanced risk of pancreatitis compared with patients with moderate hypertriglyceridaemia (HTG), and certainly in comparison with patients with normal TG levels. According to one study, in comparison with patients with normal TG levels, FCS patients had a 360-fold greater risk of acute pancreatitis, and a 23-fold greater risk compared to patients with TG values of 5-9 mmol/L (443-~800 mg/dL), underscoring the need to reduce TG in this population (Figure 2) (Gaudet et al. 2010).

**Figure 1: Clinical Outcomes in Acute Pancreatitis**

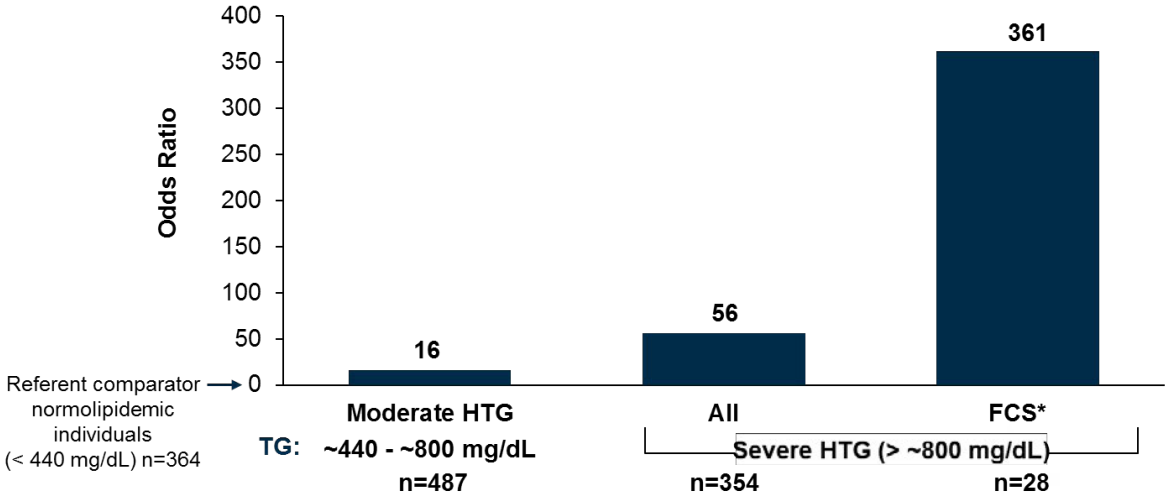



Adapted from Nawaz, *Am J Gastroenterol*, 2015.

[a] Patients were neither evaluated or diagnosed with FCS
Abbreviation: TG, triglyceride.

Abbreviations: TG = triglycerides

**Figure 2: Risk of Acute Pancreatitis Associated with Moderate and Severe Hypertriglyceridaemia Compared to Normolipidemic Controls**




Abbreviations: HTG = hypertriglyceridaemia.
Figures adapted from (Gaudet et al. 2010)

Across all aetiologies, acute pancreatitis accounts for more than 220,000 hospital admissions in the United States each year. Overall, about 20% (44,000) of patients have a severe course, and 10 to 30% of those with severe acute pancreatitis die, which translates to a mortality rate of 2 to 6%

across all causes (Whitcomb 2006). The National Pancreas Foundation estimates a slightly higher mortality rate of 10% (Foundation 2017), even with advancements in medical care. Gallstones and alcoholism are the most common cause of acute pancreatitis in the general population, although it is estimated that up to 10% of acute pancreatitis is due to SHTG (Valdivielso et al. 2014).

In another study that focused exclusively on patients admitted to a hospital with severe acute pancreatitis, Deng et al divided 176 patients into an HTG group (TGs ≥ 500 mg/dL, n = 45) and a control group (TGs < 500 mg/dL, n=131). All patients received standard, guideline-based treatments for acute pancreatitis. Compared to the control group, the HTG group had statistically worse outcomes including renal failure (51.1% vs. 16.8%), shock (37.9% vs. 14.5%), infection (37.4% vs. 18.3%) and death (13.1% vs. 9.1%) (Deng et al. 2008).

These studies examined patients presenting with acute pancreatitis from multiple causes and examined the apparent outcomes in those with HTG, but FCS patients constitute only a small fraction of all HTG patients. What distinguishes FCS patients is the nearly life-long, persistent and extreme HTG. In contrast, the vast majority of other HTG patients have secondary underlying causes such as uncontrolled diabetes, which are amenable to effective treatment, and thus for any given subject, the likelihood of recurrent acute pancreatitis is greatly diminished.

Severe and persistent HTG, although with known fluctuations, nearly always exceed 1,000 mg/dL and is the hallmark of the disease in FCS patients. However, given the low prevalence of this disease, to our knowledge, there are no well-controlled clinical studies that provide prevalence data with respect to incidence and severity of pancreatitis and outcomes, including death. Recently, a survey was conducted among 21 highly experienced lipidologists responsible for the long-term care of 251 FCS patients throughout their careers. The lipidologists reported that, in the history of their disease, recurrent abdominal pain not requiring hospitalisation occurred in 57% of patients, and led to hospitalisation that was not diagnosed as acute pancreatitis in 17% of patients. Hospitalisation for confirmed acute pancreatitis occurred in 67% of the FCS patients and half experienced recurrent acute pancreatitis with 2 to 96 lifetime hospitalisations. Twelve subjects (4.8%) died from acute pancreatitis (including children/teens aged 2, 11 and 18), with another patient dying during pregnancy. Long-term complications of recurrent acute pancreatitis, such as pancreatic insufficiency, diabetes and cardiorenal disease, accounted for 3 further deaths. Thus, total pancreatitis-related mortality was 6.0% (15/251) (Gaudet et al. 2016). The data of Nawaz et al. noted above represents mortality of those subjects who presented to the hospital with acute pancreatitis, but does not give insight into the risk per se for individual subjects. The survey data indicates that, for any given FCS subject, the risk of mortality from acute pancreatitis is ~ 6%. This is in contrast to the chylomicronemia seen by the lipidologists due to other (i.e., non-FCS) aetiologies which as noted above, once identified can usually be successfully avoided by various medical interventions. In the same survey noted above, the lipidologists were asked about the prevalence of acute pancreatitis and outcomes among patients they have followed with multifactorial (non-FCS) chylomicronemia: Among 1981 subjects reported, only 14% were hospitalised with acute pancreatitis and only 11 (0.55%) pancreatitis-related deaths were reported.

Understanding the burden of disease in FCS

The burden of disease for FCS patients has not been well characterised in the literature, mostly due to the rarity of the disease and lack of effective treatments.

Self-reported data at FCS patient meetings have elucidated the difficulty of living with FCS, including frequent and intense abdominal pain, decreased cognition, anxiety, depression, and impaired social interactions (Brown et al 2016).

Because patients' lives are punctuated by frequent episodes of abdominal pain due to chylomicronemia, their lifestyle is dominated by the need to follow an extremely fat-restricted diet and total avoidance of alcohol to avoid such episodes. This severely impacts both their daily activities at home, as well as their social life. Patients with chylomicronemia also suffer from diffuse and ill-defined arthralgias, peripheral neuropathies, hepatosplenomegaly, diffuse erythema of the skin, and eruptive xanthomas. In addition, neuropsychiatric changes have been noted in patients with chylomicronemia, including memory loss (especially for recent events), the inability to think clearly ("fuzzy thinking"), and difficulty in problem-solving (Chait et al. 1981). Such disturbances may in turn lead to lack of effective compliance with alcohol and fat-restriction.

Although not necessarily in the FCS population, Rashid et al reported patient characteristics, treatment patterns, comorbidities and risk factors associated with development of acute pancreatitis in patients with extremely high plasma triglycerides, and potential outcomes. Their retrospective analysis of 5550 patients found that 5.4% developed acute pancreatitis and concluded that patients with SHTG are often underdiagnosed, undertreated, and nonadherent to lipid-lowering therapy. The authors called for improvements in treatment options to reduce the incidence of acute pancreatitis and new economic studies to evaluate the burden of acute pancreatitis on health systems (Rashid et al. 2016).

Gardner et al reported a prospective multicentre study in 2010 that found a profound impact on the ability to work and interpersonal relationships for patients who experienced chronic pancreatitis. Data from their survey of 111 patients found that 74% of patients had their work life altered by chronic pancreatitis, 60% reported that it affected their social lives, and 46% reported that it had an effect on relationships with family and friends (Gardner et al. 2010).

The burden of FCS in the psychosocial, cognitive, and economic domains has recently been characterised in an interim analysis of an ongoing survey in FCS patients; this analysis provides insights into living with FCS and consequences on activities of daily living (Davidson 2017).

One of the most striking findings in this survey was the significant impact that FCS had on day-to-day quality of life, including psychosocial and cognitive symptoms, and the translation of this diminished quality of life and impairment on ability to work. Significant anxiety/fear and worry about multiple aspects of their disease, while not reported in all patients, had a significant impact on those in whom the symptoms were experienced.

Of note, only 22% of these adult patients in the survey are employed full time. The majority of those who are unemployed or part-time report that they have been employed before. Further, all of the patients who are unemployed feel that their unemployment status is due in part to their FCS, and 75% of them feel that their FCS is the largest reason for their current lack of employment. Of those who were employed or in school, 92% reported FCS as an impediment to fulfill responsibilities. In addition, complications of FCS caused considerable time off from work in 68% of patients who were employed ranging from 1-61 days with a mean of 30 days.

Patients report also that FCS has had an influence on career choice, with 85% reporting a moderate to significant impact, as these individuals have sought out careers with less travel and that are less demanding.

Familial chylomicronemia syndrome patients empirically learn to greatly alter their diet and lifestyle in an attempt to avoid abdominal pain and other symptoms, often to the extent of going many days without eating to "control" emerging symptoms or binging and purging. Nevertheless, momentary dietary and/or lifestyle "indiscretions," which would be innocuous to normal individuals affect the vast majority of these subjects, and debilitating abdominal pain, loss of work, hospitalisations, acute pancreatitis and even death may ensue. The awareness of a lack of effective therapy further burdens patients' mental health and quality of life. The awareness that they can transmit this to children, and possibly the fear of disease worsening during pregnancy for women, affects decisions about parenthood.

Collectively, the data currently available reinforce the higher risk of medical and psychosocial challenges affecting the physical and emotional health of FCS patients, and the enormous daily burden of disease for these patients.

Pregnancy is a major challenge for any woman with FCS, as most often, they cannot tolerate birth control pills, or estrogens, and death due to severe pancreatitis during pregnancy is well-described (Montgomery and Miller 1970, Gaudet et al. 2016).

A need still remains for additional studies to better understand and measure the disease burden from the patient's perspective. The current paucity of data limits clinician, patient and caregiver abilities to accurately assess the impact of FCS as well as the effectiveness of treatment modalities. However, premature mortality associated with poorly controlled TG levels, significant morbidity, including complications from persistent chylomicronemia such as abdominal pain, hepatomegaly, and acute pancreatitis, and psychosocial challenges of FCS have been well documented. The only other current therapeutic strategy primarily involves stringent dietary fat restriction, which is nearly impossible to follow life-long and often fails to adequately control TGs and consequently pancreatitis risk.

**Concomitant Medications in the Target Population**

Concomitant medications in the target population include:

- Other lipid-lowering agents (fibrates, fish oils, and statins)
- Pain medications (acetaminophen/paracetamol, nonsteroidal anti-inflammatory drugs [NSAIDS], and opioids)
- Platelet aggregation inhibitors
- Nutritional supplements

These concomitant medications are minimally effective in patients with FCS because their effectiveness depends, at least in part, on a functional LPL enzyme, notably deficient in these individuals. As noted earlier, standard of care is thus limited to severe dietary fat restriction, avoidance of alcohol and medications known to increase TG (Brunzell 1999-2011). Lifetime compliance with these requirements is difficult and episodes of abdominal pain and recurrent pancreatitis remain common despite dietary adherence (Gaudet et al. 2010, Ceska et al. 2016, Stroes et al. 2017). Finally, unlike many other metabolic diseases where there are external

support processes and specific products to assist in dietary compliance such as foods and labelling for gluten intolerance or phenylketonuria; in the case of FCS, dietary awareness and compliance are entirely on the shoulders of the patient.

### Important Co-morbidities Found in the Target Population

Important co-morbidities in the target population include pancreatitis and diabetes. In the Phase 3 study of patients with FCS (CS6), 76% of patients had a history of pancreatitis and 15% had a history of diabetes.

Recently presented longitudinal natural history data in 87 patients from 3 Canadian clinics (the SMASH registry) has shown that FCS patients may experience wide fluctuations in platelet count over time, ranging from mild to severe thrombocytopenia to thrombocytosis Figure 2 (Gaudet et al. 2016). The majority (55%) of FCS patients exhibited thrombocytopenia on one or more occasions when followed over prolonged periods of time, including up to 17% exhibiting values < 100 × $10^9$/L, and some as low as < 50 × $10^9$/L. In addition, 12% of FCS patients exhibited thrombocytosis (> 450 × $10^9$/L) (Table 2). In summary, there may be inherent variability in platelet counts in FCS patients (Gaudet et al. 2017).

**Table 2: Natural History of Thrombocytopenia or Thrombocytosis in Familial Chylomicronemia Syndrome (The SMASH Registry)**

| **Thrombocytopenia (Platelet count)** | **N= 87 n (%)** | **Thrombocytosis (Platelet count)** | **N= 87 n (%)** |
|---|---|---|---|
| Mild (100-149 × $10^9$/L) | 31 (35.6) | Mild (450-599 × $10^9$/L) | 6 (6.9) |
| Moderate (50-99 × $10^9$/L) | 15 (17.2) | Moderate (600–899 × $10^9$/L) | 4 (4.6) |
| Severe (<50 × $10^9$/L) | 2 (2.4) | Severe (900-1000 × $10^9$/L) | 1 (1.1) |
| Total | 48 (55.2) | Total | 11 (12.6) |

Source: (Gaudet et al. 2016)

# PART II: MODULE SII – NON-CLINICAL PART OF THE SAFETY SPECIFICATION

A summary of the important general pharmacology and nonclinical safety findings is provided below.

## General Toxicology

A comprehensive series of *in vitro* and *in vivo* studies was conducted with volanesorsen to characterise the toxicity profile of the molecule. The subcutaneous route of exposure was utilised in all *in vivo* studies for relevance to the clinical programme. The doses for each of the toxicology studies ranged from 3 to 100 mg/kg/wk in mice and 3 to 40 mg/kg/wk in monkeys and were selected to provide substantial challenge to the test animals. Low doses produced approximately clinically relevant levels of exposure. The range of doses provided no-observed-effect and/or no-observed-adverse-effect levels (NOEL, NOAEL). Adequate margins of drug exposure were achieved in each study to facilitate a risk assessment.

There were no adverse effects on reproductive function in either mice or rabbits and volanesorsen was not genotoxic. In mouse and monkey general toxicity studies, > 90% reduction of hepatic apoC-III mRNA was achieved in mice and monkeys. Reduction of apoC-III for up to 39 weeks of treatment was not associated with any findings that could be considered related to the intended pharmacologic activity.

The spectrum of changes observed in the repeat-dose toxicology studies were generally of the expected class effects of 2′-*O*-(2-methoxyethyl)-D-ribose (MOE) chimeric antisense oligonucleotide (ASO). Treatment-related effects observed in these studies were most often mild to moderate in severity and observed at the higher dose levels examined (i.e., ≥ 25 mg/kg/wk in mice and ≥ 6 mg/kg/wk in monkeys). The changes included acute and transient changes in clotting time or complement activation that were associated with high plasma oligonucleotide concentrations (primarily in monkeys). There were also decreases in platelet count observed in monkeys at ≥ 6 mg/kg/wk. In the 39-week monkey study, platelet counts < $50 \times 10^9$/L were observed in several monkeys at 6, 12, and 18 mg/kg. These reduced platelet counts recovered within 3 to 5 weeks after treatment was suspended in monkeys that were given a treatment holiday. However, monkeys that could not maintain normal platelet count upon re-initiation of treatment were terminated early. These effects on platelets are interpreted in the context of the broad database of experience with 2′-MOE ASO toxicology studies in monkeys and studies were conducted to address the potential mechanism of reduced platelet count in monkey.

Effects in target organs were attributed either to the tendency of volanesorsen to produce inflammatory responses or the accumulation of high concentrations of volanesorsen in certain organs or cell types. Some effects on tissue morphology, particularly in mice, were associated with changes in serum chemistry or haematology. Inflammatory cell infiltrates in the mouse heart led to secondary degeneration of myofibers at ≥ 50 mg/kg/wk after 26 weeks of dosing. There was increased mortality and decreased body weight in mice at 80 mg/kg/wk that were attributed to the myofiber degeneration. There was thickening of heart valves in rats. These effects were attributed to the dose-dependent inflammatory effects observed in rodent and no similar cardiac inflammation or degeneration was observed in monkeys. Effects related to repeated complement activation in monkeys led to the depletion of plasma complement component 3 (C3), and associated inflammatory changes included reduced serum albumin,

increased circulating cytokines, and inflammatory cell infiltrates in kidney or perivascular inflammation that led to early termination of selected monkeys. These effects in monkey were attributable to complement activation and are not considered relevant to humans based on the lack of complement activation in human subjects. With the exception of inflammatory effects in some tissues, little or no progression of toxicity was noted once steady-state tissue concentrations were achieved. These effects were reversible following discontinuation of treatment. The tissue distribution and plasma pharmacokinetic (PK) parameters were similar between mice and monkeys.

Table 3: Toxicity-related Information and Data

| **Key Safety Findings (from Non-clinical Studies)** | **Relevance to Human Usage** |
|---|---|
| **Toxicity** | |
| **Single-dose Toxicity**<br>Single-dose safety pharmacology studies in the monkey (cardiovascular) and mouse (neurobehavioural and pulmonary assessment studies) were performed.<br>*(See Safety Pharmacology below)*<br>**Repeat-dose Toxicity**<br>Multiple repeat dose sub-chronic (13 weeks) and chronic (up to 39 weeks) general toxicity studies in the mouse, rat and cynomolgus monkey were performed.<br>In mouse or monkey general toxicity studies, a reduction of hepatic apoC-III mRNA (> 75%) was not associated with any toxicities that were considered related to the pharmacologic inhibition of apoC-III for up to 39 weeks of treatment. Treatment-related findings in mice and monkeys were primarily consistent with those expected for the 2′-MOE-class of ASOs. | *See Safety Pharmacology below* |

| Key Safety Findings (from Non-clinical Studies) | Relevance to Human Usage |
|---|---|
| Reduction in in platelet count:<br>The most notable change in haematology parameters was a decrease in platelet count.<br>Dose and time-dependent reductions in mean platelet count were observed in monkeys in both the 3-month (40 mg/kg/wk) and 9-month studies (≥ 6 mg/kg/wk). The decrease from baseline was gradual in most monkeys, generally reaching a self-sustaining level by 13 weeks of treatment, where values typically remained well above normal haemostatic levels (> 200,000 cells/µL). In the 3-month study, a decrease (~25% relative to pre-dose values) in platelet count was observed at 40 mg/kg/wk, but not at 8 or 12 mg/kg/wk. There was, however, a subset of monkeys in the 9-month study with platelet counts < 50,000 cells/µL which was not observed in the 3-month study except for one monkey with a concurrent tail injury and abscess. This effect on platelets was not acute. Platelet counts appeared to decrease over the course of several weeks. Platelet count nadir < 50,000 cells/µL was generally observed by 16 weeks of treatment but there was 1 monkey with onset of low platelet count near the end of the 9-month treatment period. Platelet counts <50,000 cells/µL were observed in 1 of 14, 3 of 18, and 3 of 18 animals at 6, 12, and 20 mg/kg/wk, respectively. Platelet count nadirs in the five most affected monkeys range from 9,000 to 13,000 cells/µL. There were no platelet counts < 50,000 cells/µL in monkeys treated with 3 mg/kg/wk. Platelet counts < 50,000 cells/µL were generally reversible within 5 to 6 weeks following discontinuation of treatment and 4 of the 7 monkeys remained on treatment. However, platelet count decreased to < 50,000 cells/µL when treatment was resumed in some monkeys. Monkeys in which platelet count could not be maintained in the normal haemostatic range (a total of 3 monkeys treated with ≥ 12 mg/kg/wk) were terminated early.<br>There was no evidence of bone marrow cytotoxicity or damage to other haematopoietic centres at doses up to 40 mg/kg/wk for 13 weeks or up to 20 mg/kg/wk for 39 weeks of treatment. No evidence of platelet sequestration in tissues or thrombus formation was present to implicate these as contributing factors. | Reduced platelet counts were observed in humans treated with volanesorsen. In most cases, the reductions from baseline were not considered clinically significant. Two patients in Study CS6 had Grade 4 thrombocytopenia, with platelet counts < $25 \times 10^9$/L. Two patients in the extension study, CS7, also had platelet counts < $25 \times 10^9$/L.<br>Thrombocytopenia is discussed as an important identified risk in this RMP and is addressed in all relevant sections of the Summary of Product Characteristics (SmPC). |
| Pro-inflammatory effects:<br>Mononuclear cell infiltrates at the subcutaneous injection site were observed in mice, rats, and monkeys.<br>In mice, the severity and incidence of mononuclear cell infiltration at the subcutaneous injection site increased in a dose-dependent manner. Haemorrhage and/or epidermal hyperplasia (minimal to mild in severity) | Injection site reactions were commonly reported in clinical studies with volanesorsen; however, none of the adverse events (AEs) at the injection site were considered serious.<br>In the pivotal Phase 3 study (CS6) in FCS patients, 1 patient (3%) in the volanesorsen group discontinued due to an AE at the injection site. |

| Key Safety Findings (from Non-clinical Studies) | Relevance to Human Usage |
|---|---|
| were also observed at the injection site at low incidence at doses ≥ 40 mg/kg/wk at 13 weeks or at 80 mg/kg/wk at 26 weeks of treatment.<br>The extent of mononuclear/histiocytic cell infiltrates in the monkey was less than that observed in mice or rats, and the incidence and severity of changes (mononuclear/histiocytic cell infiltration, haemorrhage, oedema, and inflammation) were similar across dose groups. | |
| In addition to the inflammatory effects observed at the subcutaneous site of injection, mononuclear/histiocytic cell infiltrates and secondary changes in the heart (myofiber degeneration and valvular thickening) were observed at 80 mg/kg/wk in the mouse or 40/20 mg/kg/wk in the rat. This inflammatory pathology in rodents was correlated with increases in plasma chemokines and cytokines. In the monkey, there was no dose-dependent multi-organ cell infiltrate or cytokine/chemokine profile similar to that observed in rodents at doses up to 20 mg/kg/wk, and no pathologic alterations of the heart. Other findings in the chronic monkey study included marked increase in spleen weight, slight to moderate increase in germinal centre cellularity in lymph nodes, reductions in albumin, elevations in C-reactive protein, Immunoglobulin G, cytokines, and chemokines, and marked reduction in C3 that were attributed to the repeated weekly complement activation. | Since the findings in the heart in rodents were not observed in monkeys, and rodents are known to be more sensitive to the inflammatory effects of 2′-MOE-class of ASOs, these findings are considered rodent-specific and not relevant to humans. The mouse heart may be more sensitive to such immune cell infiltration because mice have a resident population of histiocytes in the myocardium (identifiable in the myocardial interstitium and along mural and pericardial blood vessels), which are much less apparent in hearts of humans or nonhuman primates (Treuting 2012).<br>There were no clinically relevant changes in electrocardiogram (ECG) parameters in volanesorsen-treated patients in controlled Phase 2 and 3 studies. In the pivotal Phase 3 study in FCS patients, there were no abnormal QTc findings and no study-drug related adjudicated major adverse cardiac events.<br>In a thorough QT study (CS13), treatment with volanesorsen did not prolong QTc to a clinically significant degree nor did it affect other ECG parameters including heart rate, PR or QRS intervals. |
| <u>Complement activation</u>:<br>Reversible, acute effects on complement activation were observed in monkeys at doses ≥12 mg/kg. Chronic repeated complement activation each week leads to a progressive reduction in plasma C3. In some monkeys the C3 reduction was sufficient to impair complement pathway function and was associated with inflammatory pathology that affected some blood vessels and the kidney. | These effects are common changes associated with this chemical class in the monkey (not observed in rodents or humans), and are attributed to non-specific interaction of the oligonucleotide with Factor-H, an inhibitor of the alternative complement pathway, at high plasma concentrations of drug (Shen et al. 2014), (Henry et al. 2007). Humans treated with volanesorsen did not experience alternative complement pathway activation. This finding is considered monkey-specific and not relevant to humans.<br>Chronic, repeated monkey-specific complement activation and pro-inflammatory effects are likely contributory to the perivascular changes and renal alterations in monkey and have little to no human relevance. |
| <u>Renal</u>:<br>The kidney is a target organ for distribution of the drug and contains the highest drug concentrations in both mice and monkeys. Uptake of the drug was specific for | The kidneys contain the highest concentration of volanesorsen in humans. However, there were no signs of renal abnormalities related to exposure in humans at |

| Key Safety Findings (from Non-clinical Studies) | Relevance to Human Usage |
|---|---|
| proximal tubular epithelium and there was histologic evidence of drug in these cells, but no associated degenerative changes and no effect of accumulation on renal function. There were also 4 of 18 animals in the monkey 39-week study with moderate to marked mononuclear cell infiltrates in the kidney. These were limited to the interstitium and did not disrupt tubular basement membranes, profiles, or glomerular architecture. One animal had slight interstitial fibroplasia. | the doses studied. More specifically in the pivotal Phase 3 study in FCS patients, there was no evident association between volanesorsen treatment and changes in renal function. |
| **Reproductive and Developmental Toxicity**<br>The effects of volanesorsen on fertility and/or embryo/foetal development were assessed in mice and rabbits.<br>Volanesorsen did not produce any changes in fertility in male or female mice nor any effects on embryo/foetal development at doses up to 87.5 mg/kg/wk following subcutaneous administration. No treatment-related changes in the incidence of spontaneous abortions or foetal skeletal or visceral malformations or variations were noted. In adult male animals, a 21% decrease in prostate/seminal vesicle weight and 33% reduction in sperm count were noted but there was no effect on fertility and no correlation with any microscopic changes in the testes, prostate or seminal vesicles. There were also no effects on fertility in male or female mice nor any effects on embryo/foetal development associated with hepatic reduction of apoC-III mRNA. Low concentrations of volanesorsen were measurable in placental tissue (13 ± 3 μg/g), while levels in foetal tissue were below the limit of detection (≤ 10 μg/g).<br>In rabbits, volanesorsen did not produce any changes in embryo/foetal development at doses up to 52.5 mg/kg/wk following subcutaneous administration. No treatment-related changes in the incidence of uterine implantation, foetal skeletal or visceral malformations or variations were noted. Volanesorsen produced maternal toxicity at 52.5 mg/kg/wk as manifested by reduced body weight and food consumption. The maternal toxicity led to aborted pregnancies in 3 animals and early delivery in a single animal. A slight decrease (14%) in foetal body weight was evident at the 52.5 mg/kg/wk dose group, and considered secondary to maternal toxicity. At GD 20, low concentrations of volanesorsen were measurable in placental tissue (37.4 ± 12.7 μg/g), while levels in foetal tissue were below the limit of detection (≤ 10 μg/g). | Antisense oligonucleotides, such as volanesorsen, are not transported across the placenta because of their size, molecular charge, water solubility and high plasma protein binding. However, use in pregnancy and lactation is considered to be missing information in this RMP. |
| **Safety Pharmacology**<br>Studies in monkey (cardiovascular) and mouse (neurobehavioural and pulmonary assessment studies) | There were no safety alerts for these organ systems in clinical trials. |

| Key Safety Findings (from Non-clinical Studies) | Relevance to Human Usage |
|---|---|
| No effects on parameters of cardiovascular function or body temperature were observed in the monkey.<br>No changes in pulmonary function parameters were observed in mice at single doses ≤100 mg/kg. | |
| **Genotoxicity**<br>Genotoxic potential was assessed in *in vitro* and *in vivo* assays.<br>Volanesorsen did not cause the induction of micronuclei in mouse bone marrow up to the maximum 2000 mg/kg dose level tested and did not produce increased incidence of mutations in the reverse mutation or mouse lymphoma assays up to the maximal concentrations tested. | Volanesorsen did not exhibit genotoxic potential in the studies conducted. |
| **Carcinogenicity**<br>Carcinogenicity was assessed in traditional 2-year bioassays in mice and rats. The mouse study included a mouse-active surrogate compound and there were no carcinogenic effects related to apoC-III reduction.<br>In the mouse, there was a statistically significantly increased incidence of hepatocellular adenoma, haemangiosarcoma, histiocytic sarcoma, and pituitary gland adenoma. In the rat, there was an increased incidence of malignant fibrous histiocytoma in skin at the injection site in both males and females. | Carcinogenicity studies in rat and mouse provided no clear evidence of a clinically relevant potential for carcinogenicity following 2 years of exposure to volanesorsen. The observed increased tumor incidence involved typically common mouse tumors. Furthermore, the cause of increased tumor incidence was related to the increased sensitivity of mice or rats to the inflammatory effects of 2′-MOE ASO compared to either monkeys or humans. Thus, the tumor findings in mice and rats are considered to have little to no human relevance. |

Abbreviations: AE = adverse event; apoC-III= apolipoprotein C-III; ASO = antisense oligonucleotide; C3 = component 3; ECG = electrocardiogram; FCS = Familial Chylomicronemia Syndrome; MOE = methoxyethyl; mRNA = messenger ribonucleic acid; QTc = heart rate corrected QT interval; RMP = Risk Management Plan; SmPC= Summary of Product Characteristics; wk=week

## General Pharmacology

Volanesorsen (also known as volanesorsen sodium, ISIS 304801, ApoC-III ASO) is a 2' MOE(2' *O*-[2- methoxyethyl]) antisense oligonucleotide inhibitor of the molecular target apoC-III, a key inhibitory regulator of TG metabolism.

Volanesorsen is highly bound to plasma proteins which limits glomerular filtration and urinary excretion. Greater than 97% of volanesorsen was bound to plasma proteins at clinically and toxicologically relevant concentrations (5 and 150 µg/mL) tested in mouse, monkey, and human plasma.

Volanesorsen is not a substrate for cytochrome P 450-mediated oxidative metabolism and should therefore not compete with other drugs for this metabolic pathway. In addition, volanesorsen's intracellular site of action makes it less susceptible to drug-drug interactions.

The primary route of elimination of volanesorsen, and other compounds in this chemical class, is nuclease-mediated metabolism in tissues. Once produced, these chain-shortened metabolites are rapidly eliminated in urine due to being less bound to tissue and plasma proteins (Geary 2009). Therefore, the ultimate elimination of volanesorsen is likely a combination of slow nuclease metabolism and excretion of chain-shortened metabolites, as well as remaining parent compound, in urine.

**Safety Pharmacology**

Volanesorsen has been evaluated *in vitro* in human and monkey primary hepatocytes, human HepG2 hepatoma cells, apoC-III transgenic mouse primary hepatocytes, and mice containing the human apoC-III transgene. The pharmacology of inhibiting apoC-III with species-specific ASOs was also examined in mice, rats, hamsters and monkeys.

Results show that apoC-III antisense inhibition reduces hepatic apoC-III mRNA and protein and serum apoC-III protein levels with concomitant suppression of fasting TG and very-low density lipoprotein (VLDL)-cholesterol in a dose-, drug-, concentration- and time-dependent manner in both normal and transgenic mice expressing the human apoC-III. Decreases in plasma apoC-III were consistently correlated with decreases in plasma TG. In addition, treatment increased high-density lipoprotein (HDL)-cholesterol levels and HDL functionality in cholesteryl ester transfer protein (CETP) transgenic, low density lipoprotein receptor (LDLR) -/- mice potentially through enhanced reverse cholesterol transport, and led to reductions in CETP mRNA, protein and enzymatic activity. Paraoxonase I (PON1) activity, a measure of HDL anti-oxidant capacity, also increased. This indicates that in addition to inhibiting lipase activity, apoC-III inhibits turnover of triglyceride-rich lipoproteins through a hepatic clearance mechanism mediated by the LDLR/LPR1 axis, explaining the activity observed in FCS patients which lack lipase activity (Gordts et al. 2016). Atherosclerotic plaque progression was also reduced in these mice. Volanesorsen also produced dose and time-dependent reductions of hepatic apoC-III mRNA, plasma apoC-III protein, TG, VLDL and chylomicron TG levels and increased HDL-C levels in hypertriglyceridemic rhesus monkeys. Enhanced postprandial TG clearance in mice and monkeys was also observed. Importantly, hepatic steatosis was not observed in mice and monkeys after significant reductions in apoC-III mRNA, protein and serum apoC-III protein levels.

In acute safety pharmacology studies to evaluate potential functional effects on cardiovascular, respiratory or central nervous system functions, no adverse effects were seen in any of these potential target organ systems. Volanesorsen has no effects on cardiovascular parameters (blood pressure, heart rate, electrocardiogram [ECG]) in the monkey, had no effects on neurobehavioural function in the mouse and was negative in the *in vitro* human ether-à-go-go assay. Slight and transient decreases in respiratory rate were observed in the mouse at the high dose of 250 mg/kg, but no effects were observed at doses ≤100 mg/kg. Thus, there were no major findings in the nonclinical pharmacology programme that were interpreted to indicate clinical concern.

**Table 4: Conclusions on Non-clinical Data**

| **Safety Concerns** | |
|---|---|
| Important identified risks (confirmed by clinical data) | • Thrombocytopenia/Platelet count decreased<br>• Injection site reactions. Subcutaneous administration of volanesorsen can be associated with injection site reactions |
| Important potential risks (not refuted by clinical data or which are of unknown significance) | There are no potential risks clearly identified in nonclinical studies. |
| Missing information | No additional nonclinical studies are planned. |

# PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

## SIII. 1 Brief Overview of Development

A comprehensive programme of clinical trials was conducted to evaluate volanesorsen for treatment of patients with FCS, an orphan disease.

The volanesorsen clinical development programme includes 9 clinical studies. Volanesorsen has been studied in 2 Phase 3 double-blind studies and an open-label study (CS6, a pivotal randomised, placebo-controlled, 52-week study in patients with FCS; CS16, a randomised, placebo-controlled supportive, 26-week treatment study in patients with HTG, including some patients with FCS; and CS7, an open-label follow-up study of CS6 and CS16 in patients with FCS), 2 randomised, placebo-controlled Phase 2 studies (CS2 in patients with HTG and patients with FCS and CS4 in patients with elevated TG and type 2 diabetes mellitus [T2DM]), 1 randomised, double-blind, placebo-controlled study, with an open-label extension Phase 2/3 study in patients with Familial Partial Lipodystrophy (CS17), and 2 healthy volunteer studies (CS1, a first in human randomised, placebo-controlled dose escalation study, and CS13, a thorough corrected QT study). Volanesorsen was also studied in an investigator-initiated, randomised, double-blind, placebo-controlled Phase 2 study at the National Institutes of Health in patients with familial partial lipodystrophy (CS19). This study is completed.

For the purposes of data presentation, the following pools were analysed:

- FCS Phase 2 and 3 Volanesorsen Group: all patients who received at least 1 dose of volanesorsen in Studies CS2, CS6, CS16, and CS7.
- All Volanesorsen Treated Patients in Studies CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17

## SIII. 2 Clinical Trial Exposure

As of 02 May 2021a total of 431 patients/subjects had been treated in clinical studies, including 345 patients/subjects who were treated with volanesorsen (Table 5). Overall, 95 unique FCS patients (patients who received at least one dose of volanesorsen or patients who received placebo only have been counted only once) were included in the clinical studies and 92 FCS patients were treated with volanesorsen with the starting dose of 300 mg once weekly; this dose was selected on the basis of efficacy and safety in the Phase 2 dose-ranging study. In the Phase 3 studies alone, 92 unique FCS patients have been included, 89 treated with volanesorsen. The CS7 open-label extension study had patients with extended exposure to volanesorsen beyond 12 months and, for some patients, approaching and beyond 24 months.

**Table 5: Exposure Summary**

| Study Phase / ID<br>Patient Population | Dosage Regimen / Duration | Number of Patients Treated |
|---|---|---|
| **Phase 3** | | |
| ISIS 304801-CS6<br>FCS | Volanesorsen (SC): 300 mg<br>Once weekly for 52 weeks | Volanesorsen: 33 (FCS)<br>Placebo: 33 (FCS) |
| ISIS 304801-CS7[a] | Volanesorsen (SC): 300 mg | Volanesorsen: 68 (FCS) |

| **Study Phase / ID<br>Patient Population** | **Dosage Regimen / Duration** | **Number of Patients Treated** |
|---|---|---|
| FCS | Once weekly for 52 weeks | (51 volanesorsen naïve) |
| ISIS 304801-CS16<br>HTG | Volanesorsen (SC): 300 mg<br>Once weekly for 26 weeks[b] | Volanesorsen: 75 (5 FCS)<br>Placebo: 38 (2 FCS) |
| **Phase 2** | | |
| ISIS 304801-CS2<br>Severe or Uncontrolled HTG | Volanesorsen (SC): 100, 200, 300 mg<br>Once weekly for 13 weeks | Volanesorsen: 64 (3 FCS)<br>100 mg: 13; 200 mg: 23; 300 mg: 28 (3 FCS)<br>Placebo: 24 |
| ISIS 304801-CS4<br>T2DM with HTG | Volanesorsen (SC): 300 mg<br>13 weeks: every other day for 1 week then once weekly for 12 weeks | Volanesorsen: 10<br>Placebo: 5 |
| **Phase 1** | | |
| ISIS 304801-CS1<br>Healthy Volunteers | Volanesorsen (SC):<br>SAD: 50, 100, 200, and 400 mg<br>MAD: 50, 100, 200, and 400 mg for 4 weeks: every other day for 1 week then once weekly for 3 weeks | Volanesorsen: 25<br>Placebo: 8 |
| ISIS 304801-CS13<br>Healthy Volunteers (TQTc) | Volanesorsen 300 mg SC, volanesorsen 300 mg IV, placebo, and moxifloxacin<br>Crossover study: Single doses, 1 in each of 4 treatment periods | Total: 52<br>49 dosed with volanesorsen, 46 dosed with 300 mg volanesorsen SC |
| **Phase 2/3 in FPL** | | |
| ISIS 304801-CS17<br>FPL | Volanesorsen (SC): 300 mg<br>Once weekly for 52 weeks | Volanesorsen: 33[c]<br>Placebo: 7 |
| ISIS 304801-CS19<br>FPL | Volanesorsen (SC): 300 mg<br>Once weekly for 68 weeks: 16 weeks placebo controlled, 52 weeks OLE | Volanesorsen: 2<br>Placebo: 3<br>All 5 patients enrolled continued to open-label portion of the study and received volanesorsen. |
| **All Studies** | | **431 Total<br>345 Volanesorsen<br>284 Volanesorsen 300 mg<br>86[d] Placebo<br>95 unique FCS: 92 Volanesorsen, 3 Placebo** |

Abbreviations: FCS = familial chylomicronemia syndrome; FPL = familial partial lipodystrophy; HTG = hypertriglyceridaemia; IV=intravenous; MAD = multiple ascending dose; OLE = open label extension; SAD = single ascending dose; SC = subcutaneous; T2DM = type 2 diabetes mellitus; TQTc = thorough QTc study

[a] This is an open-label study in FCS patients from CS6, CS16, or newly identified patients meeting inclusion criteria.

[b] For Study CS16, the protocol was amended so that 86 patients that had not already completed ≥ 5 months of dosing as of 27 May 2016 had dose frequency reduced to 300 mg every 2 weeks after 13 weeks of treatment.

[c] Includes 12 FPL patients who received volanesorsen in the open label extension period after completing placebo treatment in the randomized treatment period.

[d] Unique patients who received placebo only.

Summary of study drug exposure by dose and duration of exposure for FCS patients from Studies CS2, CS6, CS16, CS7 is presented in Table 6. A total of 92 unique FCS patients were treated with volanesorsen from Studies CS2, CS6, CS16, CS7. The mean duration of exposure in FCS patients was 64.18 weeks and there were a total of 113.16 patient-years of exposure to volanesorsen.

**Table 6: Summary of Exposure – Safety Set: Patients with Familial Chylomicronemia Syndrome Treated with Volanesorsen from CS2, CS6, CS16, and CS7 by Dose and Duration of Exposure**

| Parameter | 300 mg Weekly (N=40)/ Total Patient Year[a]=32.91 | 300 mg Biweekly Post AE/stopping Rule (N=49)/ Total Patient Year[a]=77.85 | 300 mg Biweekly Post W13 Cohort (N=3)/ Total Patient Year[a]=2.41 | Overall (N=92)/ Total Patient Year[a]=113.16 | Patient Year |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure – n (%) | | | | | |
| 0-13 Weeks | 11 (27.5) | 1 (2.0) | 0 | 12 (13.0) | 1.89 |
| >13-26 Weeks | 7 (17.5) | 2 (4.1) | 2 (66.7) | 11 (12.0) | 4.05 |
| >26-52 Weeks | 11 (27.5) | 8 (16.3) | 0 | 19 (20.7) | 15.52 |
| >52-78 Weeks | 3 (7.5) | 10 (20.4) | 1 (33.3) | 14 (15.2) | 16.43 |
| >78-104 Weeks | 6 (15.0) | 20 (40.8) | 0 | 26 (28.3) | 48.32 |
| >104 Weeks | 2 (5.0) | 8 (16.3) | 0 | 10 (10.9) | 26.95 |
| Number of Administration of Study Drug | | | | | |
| n | 40 | 49 | 3 | 92 | |
| Mean (SD, SE) | 41 (36, 6) | 49 (25, 4) | 33 (23, 13) | 45 (30, 3) | |
| Median (P25, P75) | 26 (13, 58) | 46 (33, 60) | 23 (17, 59) | 44 (20, 60) | |
| Min, Max | 1, 153 | 10, 123 | 17, 59 | 1, 153 | |
| Duration of exposure (Weeks)[b] | | | | | |
| n | 40 | 49 | 3 | 92 | |
| Mean (SD, SE) | 42.93 (38.26, 6.05) | 82.90 (37.19, 5.31) | 41.86 (29.82, 17.22) | 64.18 (42.19, 4.40) | |
| Median (P25, P75) | 27.64 (12.14, 60.50) | 88.43 (53.14, 102.14) | 25.14 (24.14, 76.29) | 55.57 (25.64, 100.71) | |
| Min, Max | 0.14, 155.29 | 10.14, 155.14 | 24.14, 76.29 | 0.14, 155.29 | |

Abbreviations: AE = adverse event; SD = standard deviation; SE = standard error; W = week

Note: Patients without dose adjustment in the index study but with dose adjustment in CS7 are counted in 300 mg Biweekly post AE/stopping rule cohort. Patients who received biweekly dose since the beginning of CS7 study, and patients who changed to 150 mg weekly dose in CS7 study are also included in 300 mg biweekly post AE/stopping rule cohort.

Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 -

First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].

[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[b] Duration of Exposure (days) = last volanesorsen dose date - first volanesorsen dose date + 1. Duration of exposure (weeks) = duration of exposure (days)/7.

Summary of exposure by dose and duration of exposure for FCS male and female patients is presented in Table 7 and Table 8, respectively. A total of 36 male FCS patients were treated with volanesorsen in CS2, CS6, CS16, and CS7 studies. The mean duration of exposure in male FCS patients was 58.21 weeks and there were a total of 40.16 patient-years of exposure to volanesorsen in male FCS patients. Whereas, a total of 56 female FCS patients were treated with volanesorsen in CS2, CS6, CS16, and CS7 studies and mean duration of exposure in female FCS patients was 68.02 weeks and there were a total of 73 patient-years of exposure to volanesorsen in female FCS patients.

**Table 7: Summary of Exposure – Safety Set: Patients with Familial Chylomicronemia Syndrome Treated with Volanesorsen from CS2, CS6, CS16, and CS7 by Dose and Duration of Exposure (Males)**

| Parameter | 300 mg Weekly (N=20)/ Total Patient Year[a]=17.03 | 300 mg Biweekly Post AE/stopping Rule (N=14)/ Total Patient Year[a]=21.19 | 300 mg Biweekly Post W13 Cohort (N=2)/ Total Patient Year[a]=1.94 | Overall (N=36)/ Total Patient Year[a]=40.16 | Patient Year |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure – n (%) | | | | | |
| 0-13 Weeks | 4 (20.0) | 0 | 0 | 4 (11.1) | 0.55 |
| >13-26 Weeks | 3 (15.0) | 1 (7.1) | 1 (50.0) | 5 (13.9) | 1.86 |
| >26-52 Weeks | 8 (40.0) | 3 (21.4) | 0 | 11 (30.6) | 8.74 |
| >52-78 Weeks | 2 (10.0) | 3 (21.4) | 1 (50.0) | 6 (16.7) | 7.34 |
| >78-104 Weeks | 1 (5.0) | 5 (35.7) | 0 | 6 (16.7) | 11.09 |
| >104 Weeks | 2 ( 10.0) | 2 ( 14.3) | 0 | 4 ( 11.1) | 10.59 |
| Number of Administration of Study Drug | | | | | |
| n | 20 | 14 | 2 | 36 | |
| Mean (SD, SE) | 43 (37, 8) | 43 (24, 6) | 41 (25, 18) | 43 (31, 5) | |
| Median (P25, P75) | 35 (17, 58) | 44 (25, 51) | 41 (23, 59) | 40 (22, 55) | |
| Min, Max | 1, 153 | 11, 92 | 23, 59 | 1, 153 | |
| Duration of Exposure (Weeks)[b] | | | | | |
| n | 20 | 14 | 2 | 36 | |
| Mean (SD, SE) | 44.44 (37.82, 8.46) | 78.96 (39.81, 10.64) | 50.71 (36.16, 25.57) | 58.21 (41.06, 6.84) | |
| Median (P25, P75) | 34.36 (16.14, 58.36) | 75.93 (48.14, 102.57) | 50.71 (25.14, 76.29) | 50.93 (26.14, 86.79) | |
| Min, Max | 0.14, 155.29 | 16.71, 155.14 | 25.14, 76.29 | 0.14, 155.29 | |

Abbreviations: AE = adverse event; SD = standard deviation; SE = standard error; W = week

Note: Patients without dose adjustment in the index study but with dose adjustment in CS7 are counted in 300 mg Biweekly post AE/stopping rule cohort. Patients who received biweekly dose since the beginning of CS7 study, and patients who changed to 150 mg weekly dose in CS7 study are also included in 300 mg biweekly post AE/stopping rule cohort.

Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].

[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[b] Duration of Exposure (days) = last volanesorsen dose date - first volanesorsen dose date + 1. Duration of exposure (weeks) = duration of exposure (days)/7.

**Table 8: Summary of Exposure – Safety Set: Patients with Familial Chylomicronemia Syndrome Treated with Volanesorsen from CS2, CS6, CS16, and CS7 by Dose and Duration of Exposure (Females)**

| Parameter | 300 mg Weekly (N=20)/ Total Patient Year[a]=15.87 | 300 mg Biweekly Post AE/stopping Rule (N=35)/ Total Patient Year[a]=56.66 | 300 mg Biweekly Post W13 Cohort (N=1)/ Total Patient Year[a]=0.46 | Overall (N=56)/ Total Patient Year[a]=73.00 | Patient Year |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure – n (%) | | | | | |
| 0-13 Weeks | 7 (35.0) | 1 (2.9) | 0 | 8 (14.3) | 1.34 |
| >13-26 Weeks | 4 (20.0) | 1 (2.9) | 1 (100.0) | 6 (10.7) | 2.19 |
| >26-52 Weeks | 3 (15.0) | 5 (14.3) | 0 | 8 (14.3) | 6.78 |
| >52-78 Weeks | 1 (5.0) | 7 (20.0) | 0 | 8 (14.3) | 9.09 |
| >78-104 Weeks | 5 (25.0) | 15 (42.9) | 0 | 20 (35.7) | 37.23 |
| >104 Weeks | 0 | 6 (17.1) | 0 | 6 (10.7) | 16.36 |
| Number of Administration of Study Drug | | | | | |
| n | 20 | 35 | 1 | 56 | |
| Mean (SD, SE) | 38 (35, 8) | 51 (25, 4) | 17 (NC, NC) | 46 (29, 4) | |
| Median (P25, P75) | 19 (13, 69) | 50 (33, 61) | 17 (17, 17) | 46 (19, 61) | |
| Min, Max | 1, 103 | 10, 123 | 17, 17 | 1, 123 | |
| Duration of Exposure (Weeks)[b] | | | | | |
| n | 20 | 35 | 1 | 56 | |
| Mean (SD, SE) | 41.41 (39.61, 8.86) | 84.47 (36.57, 6.18) | 24.14 (NC, NC) | 68.02 (42.82, 5.72) | |
| Median (P25, P75) | 20.14 (12.07, 79.21) | 88.57 (53.14, 102.14) | 24.14 (24.14, 24.14) | 61.43 (25.14, 102.07) | |
| Min, Max | 0.14, 103.29 | 10.14, 154.86 | 24.14, 24.14 | 0.14, 154.86 | |

Abbreviations: AE = adverse event; NC = not calculated; SD = standard deviation; SE = standard error; W = week

Note: Patients without dose adjustment in the index study but with dose adjustment in CS7 are counted in 300 mg Biweekly post AE/stopping rule cohort. Patients who received biweekly dose since the beginning of CS7 study, and patients who changed to 150 mg weekly dose in CS7 study are also included in 300 mg biweekly post AE/stopping rule cohort.

Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].

[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[b] Duration of Exposure (days) = last volanesorsen dose date - first volanesorsen dose date + 1. Duration of exposure (weeks) = duration of exposure (days)/7.

Summary of study drug exposure by time interval for all patients treated with volanesorsen from Studies CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17 is presented in Table 9. A total of 340 patients were treated with volanesorsen in Studies CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17. The mean duration of exposure in all treated patients was 28.29 weeks and there were a total of 184.34 patient-years of exposure to volanesorsen in all treated patients.

**Table 9: Summary of Study Exposure – Safety Set: All Treated Volanesorsen Patients from CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17**

| | HV-CS1 Volanesorsen | | HV-CS13 | CS2, CS4, CS6, CS7 ,CS16 and CS17 Volanesorsen[b] | | | | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Single Dose Cohort (50 to 400 mg) (N=12)/ Total Patient Year[c]=0.03** | **Multiple Dose Cohort (50 to 400 mg) (N=13)/ Total Patient Year[c]=0.74** | **Volanesorsen[a] (N=49)/ Total Patient Year[c]=0.26** | **CS2 100 mg Weekly (N=13)/ Total Patient Year[c]=2.60** | **CS2 200 mg Weekly (N=23)/ Total Patient Year[c]=4.96** | **300 mg Weekly (N=144)/ Total Patient Year[c]=71.16** | **300 mg Biweekly Post AE/ stopping Rule (N=61)/ Total Patient Year[c]=91.80** | **300 mg Biweekly Post W13 Cohort (N=25)/ Total Patient Year[c]=12.79** | (N=340)/ Total Patient Year[c]=184.34 | **Patient Year** |
| Number of Patients with Duration of Exposure – n (%) | | | | | | | | | | |
| 0-13 Weeks | 12 (100.0) | 13 (100.0) | 49 (100.0) | 13 (100.0) | 23 (100.0) | 67 ( 46.5) | 1 (1.6) | 0 | 178 (52.4) | 19.19 |
| >13-26 Weeks | 0 | 0 | 0 | 0 | 0 | 39 ( 27.1) | 5 (8.2) | 22 (88.0) | 66 (19.4) | 28.74 |
| >26-52 Weeks | 0 | 0 | 0 | 0 | 0 | 20 ( 13.9) | 11 (18.0) | 2 (8.0) | 33 (9.7) | 26.03 |
| >52 Weeks | 0 | 0 | 0 | 0 | 0 | 18 (12.5) | 44 (72.1) | 1 (4.0) | 63 (18.5) | 110.38 |
| Number of Administration of Study Drug | | | | | | | | | | |
| n | 12 | 13 | 49 | 13 | 23 | 144 | 61 | 25 | 340 | |
| Mean (SD, SE) | 1 (0, 0) | 6 (1, 0) | 2 (0, 0) | 11 (4, 1) | 12 (3, 1) | 28 (27, 2) | 48 (25, 3) | 21 (8, 2) | 24 (25, 1) | |
| Median (P25, P75) | 1 (1, 1) | 6 (6, 6) | 2 (2, 2) | 13 (12, 13) | 13 (12, 13) | 19 (13, 43) | 45 (29, 60) | 20 (19, 22) | 13 (6, 33) | |
| Min, Max | 1, 1 | 3, 6 | 1, 2 | 2, 13 | 1, 13 | 1, 153 | 10, 123 | 13, 59 | 1, 153 | |

| | HV-CS1 Volanesorsen | | HV-CS13 | CS2, CS4, CS6, CS7 ,CS16 and CS17 Volanesorsen[b] | | | | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Single Dose Cohort (50 to 400 mg) (N=12)/ Total Patient Year[c]=0.03** | **Multiple Dose Cohort (50 to 400 mg) (N=13)/ Total Patient Year[c]=0.74** | **Volanesorsen[a] (N=49)/ Total Patient Year[c]=0.26** | **CS2 100 mg Weekly (N=13)/ Total Patient Year[c]=2.60** | **CS2 200 mg Weekly (N=23)/ Total Patient Year[c]=4.96** | **300 mg Weekly (N=144)/ Total Patient Year[c]=71.16** | **300 mg Biweekly Post AE/ stopping Rule (N=61)/ Total Patient Year[c]=91.80** | **300 mg Biweekly Post W13 Cohort (N=25)/ Total Patient Year[c]=12.79** | (N=340)/ Total Patient Year[c]=184.34 | **Patient Year** |
| Duration of Exposure (Weeks)[d] | | | | | | | | | | |
| n | 12 | 13 | 49 | 13 | 23 | 144 | 61 | 25 | 340 | |
| Mean (SD, SE) | 0.14 (0.00, 0.00) | 2.96 (0.67, 0.19) | 0.28 (0.05, 0.01) | 10.43 (4.12, 1.14) | 11.24 (2.70, 0.56) | 25.79 (26.84, 2.24) | 78.52 (37.12, 4.75) | 26.70 (10.37, 2.07) | 28.29 (34.81, 1.89) | |
| Median (P25, P75) | 0.14 (0.14, 0.14) | 3.14 (3.14, 3.14) | 0.29 (0.29, 0.29) | 12.14 (12.00, 12.14) | 12.14 (12.00, 12.14) | 14.64 (11.93, 27.64) | 76.14 (50.57, 102.00) | 24.29 (24.14, 25.14) | 12.29 (3.14, 37.86) | |
| Min, Max | 0.14, 0.14 | 0.71, 3.14 | 0.14, 0.43 | 1.14, 12.14 | 0.14, 12.29 | 0.14, 155.29 | 10.14, 155.14 | 23.14, 76.29 | 0.14, 155.29 | |

Abbreviations: HV = healthy volunteers; AE = adverse event; IV= intravenous; PO = oral; SD = standard deviation; SC =subcutaneous; SE = standard error; W = week

Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].

[a] CS13 was a 4-way crossover study. Patients received 300 mg volanesorsen IV / placebo SC, 300 mg volanesorsen SC / placebo IV, 400 mg moxifloxacin PO / placebo IV + placebo SC, placebo IV / placebo SC in each treatment period with a minimum of 7-day washout. CS13 volanesorsen duration of exposure and number of administration are based on the treatment received during each treatment period.

[b] CS2 Safety Set is defined as all randomized patients who received at least 1 injection.

[c] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[d] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of Volanesorsen in open label extension period is counted.

Summary of study exposure for all treated volanesorsen patients from Studies CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17 for males and females is presented in Table 10 and Table 11, respectively. A total of 193 male patients were treated with volanesorsen in CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17 studies. The mean duration of exposure in all treated male patients was 21.33 weeks and there were a total of 78.90 patient-years of exposure to volanesorsen. Whereas, a total of 147 female patients were treated with volanesorsen in CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17 studies. The mean duration of exposure in in all treated female patients was 37.43 weeks and there were a total of 105.45 patient-years of exposure to volanesorsen.

**Table 10: Summary of Study Exposure – Safety Set: All Treated Volanesorsen Patients from CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17 (Males)**

| | HV-CS1 Volanesorsen | | HV-CS13 | CS2, CS4, CS6, CS7 ,CS16 and CS17 Volanesorsen[b] | | | | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | Single Dose Cohort (50 to 400 mg) (N=12)/ Total Patient Year[c]=0.03 | Multiple Dose Cohort (50 to 400 mg) (N=13)/ Total Patient Year[c]=0.74 | Volanesorsen[a] (N=23)/ Total Patient Year[c]=0.13 | CS2 100 mg Weekly (N=8)/ Total Patient Year[c]=1.65 | CS2 200 mg Weekly (N=20)/ Total Patient Year[c]=4.26 | 300 mg Weekly (N=79)/ Total Patient Year[c]=37.06 | 300 mg Biweekly Post AE/ stopping Rule (N=19)/ Total Patient Year[c]=25.13 | 300 mg Biweekly Post W13 Cohort (N=19)/ Total Patient Year[c]=9.91 | (N=193)/ Total Patient Year[c]=78.90 | Patient Year |
| Number of Patients with Duration of Exposure – n (%) | | | | | | | | | | |
| 0-13 Weeks | 12 (100.0) | 13 (100.0) | 23 (100.0) | 8 (100.0) | 20 (100.0) | 32 ( 40.5) | 0 | 0 | 108 (56.0) | 12.20 |
| >13-26 Weeks | 0 | 0 | 0 | 0 | 0 | 29 ( 36.7) | 4 (21.1) | 18 (94.7) | 51 (26.4) | 22.68 |
| >26-52 Weeks | 0 | 0 | 0 | 0 | 0 | 13 ( 16.5) | 3 (15.8) | 0 | 16 (8.3) | 12.46 |
| >52 Weeks | 0 | 0 | 0 | 0 | 0 | 5 (6.3) | 12 (63.2) | 1 (5.3) | 18 (9.3) | 31.56 |
| Number of Administration of Study Drug | | | | | | | | | | |
| n | 12 | 13 | 23 | 8 | 20 | 79 | 19 | 19 | 193 | |
| Mean (SD, SE) | 1 (0, 0) | 6 (1, 0) | 2 (0, 0) | 12 (4, 1) | 12 (3, 1) | 26 (25, 3) | 39 (23, 5) | 22 (9, 2) | 19 (21, 2) | |
| Median (P25, P75) | 1 (1, 1) | 6 (6, 6) | 2 (2, 2) | 13 (13, 13) | 13 (12, 13) | 20 (13, 26) | 34 (18, 51) | 20 (19, 22) | 13 (6, 24) | |
| Min, Max | 1, 1 | 3, 6 | 1, 2 | 2, 13 | 1, 13 | 1, 153 | 11, 92 | 13, 59 | 1, 153 | |
| Duration of Exposure (Weeks)[d] | | | | | | | | | | |
| n | 12 | 13 | 23 | 8 | 20 | 79 | 19 | 19 | 193 | |
| Mean (SD, SE) | 0.14 (0.00, 0.00) | 2.96 (0.67, 0.19) | 0.29 (0.06, 0.01) | 10.73 (3.88, 1.37) | 11.11 (2.88, 0.64) | 24.48 (23.78, 2.67) | 69.02 (39.44, 9.05) | 27.21 (11.90, 2.73) | 21.33 (27.24, 1.96) | |
| Median (P25, P75) | 0.14 (0.14, 0.14) | 3.14 (3.14, 3.14) | 0.29 (0.29, 0.29) | 12.14 (12.00, 12.14) | 12.14 (12.07, 12.14) | 20.29 (12.14, 25.29) | 60.57 (39.14, 100.00) | 24.29 (24.14, 25.14) | 12.14 (3.14, 25.14) | |
| Min, Max | 0.14, 0.14 | 0.71, 3.14 | 0.14, 0.43 | 1.14, 12.14 | 0.14, 12.29 | 0.14, 155.29 | 16.71, 155.14 | 23.14, 76.29 | 0.14, 155.29 | |

Abbreviations: HV = healthy volunteers; AE = adverse event; IV= intravenous; PO = oral; SD = standard deviation; SC =subcutaneous; SE = standard error; W = week
Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First

Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].

[a] CS13 was a 4-way crossover study. Patients received 300 mg volanesorsen IV / placebo SC, 300 mg volanesorsen SC / placebo IV, 400 mg moxifloxacin PO / placebo IV + placebo SC, placebo IV / placebo SC in each treatment period with a minimum of 7-day washout. CS13 volanesorsen duration of exposure and number of administration are based on the treatment received during each treatment period.

[b] CS2 Safety Set is defined as all randomized patients who received at least 1 injection.

[c] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[d] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of volanesorsen in open label extension period is counted.

**Table 11: Summary of Study Exposure – Safety Set: All Treated Volanesorsen Patients from CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS 17 (Females)**

| | HV-CS1 Volanesorsen | | HV-CS13 | CS2, CS4, CS6, CS7 ,CS16 and CS17 Volanesorsen[b] | | | Overall | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | Single Dose Cohort (50 to 400 mg) (N=0)/ Total Patient Year[c]=0 | Multiple Dose Cohort (50 to 400 mg) (N=0)/ Total Patient Year[c]=0 | Volanesorsen[a] (N=26)/ Total Patient Year[c]=0.14 | CS2 100 mg Weekly (N=5)/ Total Patient Year[c]=0.95 | CS2 200 mg Weekly (N=3)/ Total Patient Year[c]=0.70 | 300 mg Weekly (N=65)/ Total Patient Year[c]=34.10 | 300 mg Biweekly Post AE/ stopping Rule (N=42)/ Total Patient Year[c]=66.67 | 300 mg Biweekly Post W13 Cohort (N=6)/ Total Patient Year[c]=2.89 | (N=147)/ Total Patient Year[c]=105.45 | Patient Year |
| Number of Patients with Duration of Exposure – n (%) | | | | | | | | | | |
| 0-13 Weeks | 0 | 0 | 26 (100.0) | 5 (100.0) | 3 (100.0) | 35 (53.8) | 1 (2.4) | 0 | 70 (47.6) | 6.99 |
| >13-26 Weeks | 0 | 0 | 0 | 0 | 0 | 10 (15.4) | 1 (2.4) | 4 (66.7) | 15 (10.2) | 6.06 |
| >26-52 Weeks | 0 | 0 | 0 | 0 | 0 | 7 (10.8) | 8 (19.0) | 2 (33.3) | 17 (11.6) | 13.57 |
| >52 Weeks | 0 | 0 | 0 | 0 | 0 | 13 (20.0) | 32 (76.2) | 0 | 45 (30.6) | 78.83 |
| Number of Administration of Study Drug | | | | | | | | | | |
| n | 0 | 0 | 26 | 5 | 3 | 65 | 42 | 6 | 147 | |
| Mean (SD, SE) | NC (NC, NC) | NC (NC, NC) | 2 (0, 0) | 10 (5, 2) | 13 (0, 0) | 31 (29, 4) | 52 (25, 4) | 19 (3, 1) | 30 (29, 2) | |
| Median (P25, P75) | NC (NC, NC) | NC (NC, NC) | 2 (2, 2) | 12 (9, 13) | 13 (13, 13) | 15 (12, 50) | 50 (33, 63) | 20 (17, 21) | 18 (5, 50) | |
| Min, Max | NC, NC | NC, NC | 1, 2 | 2, 13 | 13, 13 | 1, 112 | 10, 123 | 15, 23 | 1, 123 | |
| Duration of Exposure (Weeks)[d] | | | | | | | | | | |
| n | 0 | 0 | 26 | 5 | 3 | 65 | 42 | 6 | 147 | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Mean (SD, SE) | NC (NC, NC) | NC (NC, NC) | 0.27 (0.04, 0.01) | 9.94 (4.92, 2.20) | 12.14 (0.14, 0.08) | 27.38 (30.27, 3.76) | 82.83 (35.67, 5.50) | 25.10 (1.48, 0.60) | 37.43 (41.09, 3.39) |
| Median (P25, P75) | NC (NC, NC) | NC (NC, NC) | 0.29 (0.29, 0.29) | 12.14 (12.14, 12.14) | 12.14 (12.00, 12.29) | 12.14 (9.14, 41.29) | 84.00 (52.43, 102.14) | 24.21 (24.14, 26.29) | 18.14 (3.14, 59.14) |
| Min, Max | NC, NC | NC, NC | 0.14, 0.29 | 1.14, 12.14 | 12.00, 12.29 | 0.14, 103.29 | 10.14, 154.86 | 24.14, 27.57 | 0.14, 154.86 |

Abbreviations: HV = healthy volunteers; AE = adverse event; IV= intravenous; PO = oral; NC = not calculated; SD = standard deviation; SC =subcutaneous; SE = standard error; W = week

Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].

[a] CS13 was a 4-way crossover study. Patients received 300 mg volanesorsen IV / placebo SC, 300 mg volanesorsen SC / placebo IV, 400 mg moxifloxacin PO / placebo IV + placebo SC, placebo IV / placebo SC in each treatment period with a minimum of 7-day washout. CS13 volanesorsen duration of exposure and number of administration are based on the treatment received during each treatment period.

[b] CS2 Safety Set is defined as all randomized patients who received at least 1 injection.

[c] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[d] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of Volanesorsen in open label extension period is counted.

Summary of study drug exposure by time interval for all patients treated in CS17 study is presented in Table 12. A total of 33 patients were treated with volanesorsen in CS17 study. The mean duration of exposure for all patients treated in CS17 study was 47.32 weeks and there were a total of 29.93 patient-years of exposure to volanesorsen.

**Table 12: Summary of Study Drug Exposure – Safety Set: All Treated Volanesorsen Patients from CS17**

| Parameter | 300 mg Weekly (N=24)/ Total Patient Year[a]=17.38 | 300 mg Biweekly (N=9)/ Total Patient Year[a]=12.54 | Overall (N=33)/ Total Patient Year[a]=29.93 | Patient Year |
|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | |
| 0 - 13 Weeks | 4 (16.7) | 0 | 4 (12.1) | 0.32 |
| >13 - 26 Weeks | 4 (16.7) | 0 | 4 (12.1) | 1.45 |
| >26 - 52 Weeks | 9 (37.5) | 3 (33.3) | 12 (36.4) | 9.48 |
| >52 Weeks | 7 (29.2) | 6 (66.7) | 13 (39.4) | 18.68 |
| Number of Administration of Study Drug | | | | |
| n | 24 | 9 | 33 | |
| Mean (SD, SE) | 54 (22, 4) | 52 (25, 8) | 54 (22, 4) | |
| Median (P25, P75) | 52 (44, 70) | 44 (29, 64) | 50 (43, 69) | |
| Min, Max | 8, 112 | 27, 92 | 8, 112 | |
| Duration of Exposure (Weeks)[b] | | | | |
| n | 24 | 9 | 33 | |
| Mean (SD, SE) | 37.79 (24.15, 4.93) | 72.73 (28.06, 9.35) | 47.32 (29.42, 5.12) | |
| Median (P25, P75) | 36.36 (19.71, 56.07) | 64.29 (50.57, 72.29) | 46.86 (29.00, 61.14) | |
| Min, Max | 0.86, 88.43 | 46.86, 123.43 | 0.86, 123.43 | |

Abbreviations: SD = standard deviation; SE = standard error

[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[b] CS17 has two treatment period, randomized treatment period (up to Week 52) and open-label extension period (on or after Week 53). In randomized treatment period, if the last dose of volanesorsen is given weekly, exposure duration is the minimum of [(Last Dose Date - First Dose Date + 7) + (Last Dose Date - First Dose Date + 1)] and [Last Dose Date - First Dose Date + 1]. If the last dose of volanesorsen is given biweekly, exposure duration is the minimum of [(Last Dose Date - First Dose Date + 14) + {Last Dose Date - First Dose Date + 1)] and [Last Dose Date - First Dose Date + 1]. In open-label extension period, duration of exposure = Last Dose Date - First Dose Date + 1. The total duration is the summation of the duration in each period. Duration of Exposure (weeks) = Duration of Exposure (days)/7.

Summary of study drug exposure for males and females in all treated volanesorsen patients from CS17 is presented in Table 13 and Table 14 respectively. A total of 10 male patients were treated with volanesorsen in CS17 study. The mean duration of exposure in all treated male patients from CS17 was 37.13 weeks and there were a total of 7.12 patient-years of exposure to volanesorsen. Whereas, a total of 23 female patients were treated with volanesorsen in CS17 study. The mean duration of exposure in all treated female patients from CS17 was 51.75 weeks and there were a total of 22.81 patient-years of exposure to volanesorsen.

**Table 13: Summary of Study Drug Exposure – Safety Set: All Treated Volanesorsen Patients from CS17 (Males)**

| Parameter | 300 mg Weekly (N=8)/ Total Patient Year[a]=4.58 | 300 mg Biweekly (N=2)/ Total Patient Year[a]=2.54 | Overall (N=10)/ Total Patient Year[a]=7.12 | Overall Patient Year |
|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | |
| 0 - 13 Weeks | 1 (12.5) | 0 | 1 (10.0) | 0.18 |
| >13 - 26 Weeks | 2 (25.0) | 0 | 2 (20.0) | 0.68 |
| >26 - 52 Weeks | 5 (62.5) | 0 | 5 (50.0) | 3.72 |
| >52 Weeks | 0 | 2 (100.0) | 2 (20.0) | 2.54 |
| Number of Administration of Study Drug | | | | |
| n | 8 | 2 | 10 | |
| Mean (SD, SE) | 50 (22, 8) | 41 (18, 13) | 48 (21, 7) | |
| Median (P25, P75) | 50 (39, 68) | 41 (28, 54) | 50 (35, 66) | |
| Min, Max | 8, 76 | 28, 54 | 8, 76 | |
| Duration of Exposure (Weeks)[b] | | | | |
| n | 8 | 2 | 10 | |
| Mean (SD, SE) | 29.88 (14.15, 5.00) | 66.14 (7.88, 5.57) | 37.13 (19.91, 6.30) | |
| Median (P25, P75) | 30.29 (17.71, 43.71) | 66.14 (60.57, 71.71) | 36.36 (20.29, 46.29) | |
| Min, Max | 9.29, 46.29 | 60.57, 71.71 | 9.29, 71.71 | |

Abbreviations: SD = standard deviation; SE = standard error

[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[b] CS17 has two treatment period, randomized treatment period (up to Week 52) and open-label extension period (on or after Week 53). In randomized treatment period, if the last dose of volanesorsen is given weekly, exposure duration is the minimum of [(Last Dose Date - First Dose Date + 7) + (Last Dose Date - First Dose Date + 1)] and [Last Dose Date - First Dose Date + 1]. If the last dose of volanesorsen is given biweekly, exposure duration is the minimum of [(Last Dose Date - First Dose Date + 14) + {Last Dose Date - First Dose Date + 1)] and [Last Dose Date - First Dose Date + 1]. In open-label extension period, duration of exposure = Last Dose Date - First Dose Date + 1. The total duration is the summation of the duration in each period. Duration of Exposure (weeks) = Duration of Exposure (days)/7.

## Table 14: Summary of Study Drug Exposure – Safety Set: All Treated Volanesorsen Patients from CS17 (Females)

| Parameter | 300 mg Weekly (N=16)/ Total Patient Year[a]=12.80 | 300 mg Biweekly (N=7)/ Total Patient Year[a]=10.01 | Overall (N=23)/ Total Patient Year[a]=22.81 | Patient Year |
|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | |
| 0 - 13 Weeks | 3 (18.8) | 0 | 3 (13.0) | 0.14 |
| >13 - 26 Weeks | 2 (12.5) | 0 | 2 (8.7) | 0.77 |
| >26 - 52 Weeks | 4 (25.0) | 3 ( 42.9) | 7 (30.4) | 5.75 |
| >52 Weeks | 7 (43.8) | 4 ( 57.1) | 11 (47.8) | 16.15 |
| Number of Administration of Study Drug | | | | |
| n | 16 | 7 | 23 | |
| Mean (SD, SE) | 57 (22, 5) | 55 (27, 10) | 56 (23, 5) | |
| Median (P25, P75) | 52 (46, 72) | 44 (29, 89) | 50 (43, 72) | |
| Min, Max | 19, 112 | 27, 92 | 19, 112 | |
| Duration of Exposure (Weeks)[b] | | | | |
| n | 16 | 7 | 23 | |
| Mean (SD, SE) | 41.75 (27.39, 6.85) | 74.61 (31.95, 12.08) | 51.75 (32.08, 6.69) | |
| Median (P25, P75) | 46.36 (20.14, 59.64) | 64.29 (49.57, 115.29) | 51.43 (30.00, 70.00) | |
| Min, Max | 0.86, 88.43 | 46.86, 123.43 | 0.86, 123.43 | |

Abbreviations: SD = standard deviation; SE = standard error

[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[b] CS17 has two treatment period, randomized treatment period (up to Week 52) and open-label extension period (on or after Week 53). In randomized treatment period, if the last dose of volanesorsen is given weekly, exposure duration is the minimum of [(Last Dose Date - First Dose Date + 7) + (Last Dose Date - First Dose Date + 1)] and [Last Dose Date - First Dose Date + 1]. If the last dose of volanesorsen is given biweekly, exposure duration is the minimum of [(Last Dose Date - First Dose Date + 14) + {Last Dose Date - First Dose Date + 1)] and [Last Dose Date - First Dose Date + 1]. In open-label extension period, duration of exposure = Last Dose Date - First Dose Date + 1. The total duration is the summation of the duration in each period. Duration of Exposure (weeks) = Duration of Exposure (days)/7.

Summary of study drug exposure by time interval and by ethnicity for all patients treated with volanesorsen from CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17 is presented in Table 15 and Table 16. A total of 44 hispanic or latino patients were treated with volanesorsen in CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17 studies, the mean duration of exposure in hispanic or latino ethinicity was 19.02 weeks and there were a total of 16.04 patient-years of exposure to volanesorsen. Whereas in not hispanic or latino ethnicity from CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17 studies, a total of 296 not hispanic or latino patients were treated with volanesorsen and the mean duration of exposure was 29.67 weeks and there were a total of 168.31 patient-years of exposure to volanesorsen.

**Table 15: Summary of Study Drug Exposure – Safety Set: All Treated Volanesorsen Patients from CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17 (Hispanic or Latino)**

| | HV-CS1 Volanesorsen | | HV-CS13 | CS2, CS4, CS6, CS7 ,CS16 and CS17 Volanesorsen[b] | | | | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | Single Dose Cohort (50 to 400 mg) (N=3)/ Total Patient Year[c]=0.01 | Multiple Dose Cohort (50 to 400 mg) (N=3)/ Total Patient Year[c]=0.18 | Volanesorsen [a] (N=14)/ Total Patient Year[c]=0.08 | CS2 100 mg Weekly (N=0)/ Total Patient Year[c]=0 | CS2 200 mg Weekly (N=0)/ Total Patient Year[c]=0 | 300 mg Weekly (N=15)/ Total Patient Year[c]=5.86 | 300 mg Biweekly Post AE/ stopping Rule (N=8)/ Total Patient Year[c]=9.45 | 300 mg Biweekly Post W13 Cohort (N=1)/ Total Patient Year[c]=0.46 | (N=44)/ Total Patient Year[c]=16.04 | Patient Year |
| Number of Patients with Duration of Exposure - n(%) | | | | | | | | | | |
| 0 - 13 Weeks | 3 (100.0) | 3 (100.0) | 14 (100.0) | 0 | 0 | 10 (66.7) | 0 | 0 | 30 (68.2) | 2.30 |
| >13 - 26 Weeks | 0 | 0 | 0 | 0 | 0 | 2 (13.3) | 1 (12.5) | 1 (100.0) | 4 (9.1) | 1.57 |
| >26 - 52 Weeks | 0 | 0 | 0 | 0 | 0 | 2 (13.3) | 2 (25.0) | 0 | 4 (9.1) | 3.56 |
| >52 Weeks | 0 | 0 | 0 | 0 | 0 | 1 (6.7) | 5 (62.5) | 0 | 6 (13.6) | 8.59 |
| Number of Administration of Study Drug | | | | | | | | | | |
| n | 3 | 3 | 14 | 0 | 0 | 15 | 8 | 1 | 44 | |
| Mean (SD, SE) | 1 (0, 0) | 6 (0, 0) | 2 (0, 0) | NC (NC, NC) | NC (NC, NC) | 21 (15, 4) | 39 (19, 7) | 23 (NC, NC) | 16 (18, 3) | |
| Median (P25, P75) | 1 (1, 1) | 6 (6, 6) | 2 (2, 2) | NC (NC, NC) | NC (NC, NC) | 15 (13, 20) | 42 (23, 54) | 23 (23, 23) | 11 (2, 19) | |
| Min, Max | 1, 1 | 6, 6 | 1, 2 | NC, NC | NC, NC | 7, 51 | 12, 63 | 23, 23 | 1, 63 | |

| | HV-CS1 Volanesorsen | | HV-CS13 | CS2, CS4, CS6, CS7 ,CS16 and CS17 Volanesorsen[b] | | | | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Single Dose Cohort (50 to 400 mg) (N=3)/ Total Patient Year[c]=0.01** | **Multiple Dose Cohort (50 to 400 mg) (N=3)/ Total Patient Year[c]=0.18** | **Volanesorsen [a] (N=14)/ Total Patient Year[c]=0.08** | **CS2 100 mg Weekly (N=0)/ Total Patient Year[c]=0** | **CS2 200 mg Weekly (N=0)/ Total Patient Year[c]=0** | **300 mg Weekly (N=15)/ Total Patient Year[c]=5.86** | **300 mg Biweekly Post AE/ stopping Rule (N=8)/ Total Patient Year[c]=9.45** | **300 mg Biweekly Post W13 Cohort (N=1)/ Total Patient Year[c]=0.46** | **(N=44)/ Total Patient Year[c]=16.04** | **Patient Year** |
| Duration of Exposure (Weeks)[d] | | | | | | | | | | |
| n | 3 | 3 | 14 | 0 | 0 | 15 | 8 | 1 | 44 | |
| Mean (SD, SE) | 0.14 (0.00, 0.00) | 3.14 (0.00, 0.00) | 0.29 (0.06, 0.01) | NC (NC, NC) | NC (NC, NC) | 20.37 (17.24, 4.45) | 61.64 (28.66, 10.13) | 24.14 (NC, NC) | 19.02 (26.95, 4.06) | |
| Median (P25, P75) | 0.14 (0.14, 0.14) | 3.14 (3.14, 3.14) | 0.29 (0.29, 0.29) | NC (NC, NC) | NC (NC, NC) | 12.14 (12.00, 22.14) | 58.43 (41.71, 88.57) | 24.14 (24.14, 24.14) | 8.64 (0.29, 23.14) | |
| Min, Max | 0.14, 0.14 | 3.14, 3.14 | 0.14, 0.43 | NC, NC | NC, NC | 4.14, 55.43 | 16.71, 99.00 | 24.14, 24.14 | 0.14, 99.00 | |

Abbreviations: HV = healthy volunteers; AE = adverse event; IV= intravenous; PO = oral; SD = standard deviation; SC =subcutaneous; SE = standard error; W = week
Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].
[a] CS13 was a 4-way crossover study. Patients received 300 mg volanesorsen IV / placebo SC, 300 mg volanesorsen SC / placebo IV, 400 mg moxifloxacin PO / placebo IV + placebo SC, placebo IV / placebo SC in each treatment period with a minimum of 7-day washout. CS13 volanesorsen duration of exposure and number of administration are based on the treatment received during each treatment period.
[b] CS2 Safety Set is defined as all randomized patients who received at least 1 injection.
[c] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[d] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of volanesorsen in open label extension period is counted.

**Table 16: Summary of Study Drug Exposure – Safety Set: All Treated Volanesorsen Patients from CS1, CS13, CS2, CS4, CS6, CS7, CS16 and CS17 (Not Hispanic or Latino)**

| | HV-CS1 Volanesorsen | | HV-CS13 | CS2, CS4, CS6, CS7 ,CS16 and CS17 Volanesorsen[b] | | | | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | Single Dose Cohort (50 to 400 mg) (N=9)/ Total Patient Year[c]=0.02 | Multiple Dose Cohort (50 to 400 mg) (N=10)/ Total Patient Year[c]=0.56 | Volanesorsen[a] (N=35)/ Total Patient Year[c]=0.19 | CS2 100 mg Weekly (N=13)/ Total Patient Year[c]=2.60 | CS2 200 mg Weekly (N=23)/ Total Patient Year[c]=4.96 | 300 mg Weekly (N=129)/ Total Patient Year[c]=65.31 | 300 mg Biweekly Post AE/ stopping Rule (N=53)/ Total Patient Year[c]=82.35 | 300 mg Biweekly Post W13 Cohort (N=24)/ Total Patient Year[c]=12.33 | (N=296)/ Total Patient Year[c]=168.31 | Patient Year |
| Number of Patients with Duration of Exposure - n(%) | | | | | | | | | | |
| 0 - 13 Weeks | 9 (100.0) | 10 (100.0) | 35 (100.0) | 13 (100.0) | 23 (100.0) | 57 (44.2) | 1 (1.9) | 0 | 148 (50.0) | 16.89 |
| >13 - 26 Weeks | 0 | 0 | 0 | 0 | 0 | 37 (28.7) | 4 (7.5) | 21 (87.5) | 62 (20.9) | 27.16 |
| >26 - 52 Weeks | 0 | 0 | 0 | 0 | 0 | 18 (14.0) | 9 (17.0) | 2 (8.3) | 29 (9.8) | 22.46 |
| >52 Weeks | 0 | 0 | 0 | 0 | 0 | 17 (13.2) | 39 (73.6) | 1 (4.2) | 57 (19.3) | 101.79 |
| Number of Administration of Study Drug | | | | | | | | | | |
| n | 9 | 10 | 35 | 13 | 23 | 129 | 53 | 24 | 296 | |
| Mean (SD, SE) | 1 (0, 0) | 6 (1, 0) | 2 (0, 0) | 11 (4, 1) | 12 (3, 1) | 29 (28, 2) | 49 (26, 4) | 21 (8, 2) | 25 (26, 2) | |
| Median (P25, P75) | 1 (1, 1) | 6 (6, 6) | 2 (2, 2) | 13 (12, 13) | 13 (12, 13) | 20 (13, 43) | 45 (29, 61) | 20 (19, 22) | 14 (6, 33) | |
| Min, Max | 1, 1 | 3, 6 | 1, 2 | 2, 13 | 1, 13 | 1, 153 | 10, 123 | 13, 59 | 1, 153 | |
| Duration of Exposure (Weeks)[d] | | | | | | | | | | |
| n | 9 | 10 | 35 | 13 | 23 | 129 | 53 | 24 | 296 | |
| Mean (SD, SE) | 0.14 (0.00, 0.00) | 2.90 (0.77, 0.24) | 0.28 (0.05, 0.01) | 10.43 (4.12, 1.14) | 11.24 (2.70, 0.56) | 26.42 (27.73, 2.44) | 81.07 (37.80, 5.19) | 26.81 (10.58, 2.16) | 29.67 (35.66, 2.07) | |

| | HV-CS1 Volanesorsen | | HV-CS13 | CS2, CS4, CS6, CS7 ,CS16 and CS17 Volanesorsen[b] | | | | | Overall | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Single Dose Cohort (50 to 400 mg) (N=9)/ Total Patient Year[c]=0.02** | **Multiple Dose Cohort (50 to 400 mg) (N=10)/ Total Patient Year[c]=0.56** | **Volanesorsen [a] (N=35)/ Total Patient Year[c]=0.19** | **CS2 100 mg Weekly (N=13)/ Total Patient Year[c]=2.60** | **CS2 200 mg Weekly (N=23)/ Total Patient Year[c]=4.96** | **300 mg Weekly (N=129)/ Total Patient Year[c]=65.31** | **300 mg Biweekly Post AE/ stopping Rule (N=53)/ Total Patient Year[c]=82.35** | **300 mg Biweekly Post W13 Cohort (N=24)/ Total Patient Year[c]=12.33** | **(N=296)/ Total Patient Year[c]=168.31** | **Patient Year** |
| Median (P25, P75) | 0.14 (0.14, 0.14) | 3.14 (3.14, 3.14) | 0.29 (0.29, 0.29) | 12.14 (12.00, 12.14) | 12.14 (12.00, 12.14) | 18.14 (11.86, 28.14) | 80.29 (51.00, 102.29) | 24.29 (24.14, 25.14) | 12.93 (3.14, 40.14) | |

Abbreviations: HV = healthy volunteers; AE = adverse event; IV= intravenous; PO = oral; SD = standard deviation; SC =subcutaneous; SE = standard error; W = week
Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].
[a] CS13 was a 4-way crossover study. Patients received 300 mg volanesorsen IV / placebo SC, 300 mg volanesorsen SC / placebo IV, 400 mg moxifloxacin PO / placebo IV + placebo SC, placebo IV / placebo SC in each treatment period with a minimum of 7-day washout. CS13 volanesorsen duration of exposure and number of administration are based on the treatment received during each treatment period.
[b] CS2 Safety Set is defined as all randomized patients who received at least 1 injection.
[c] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[d] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of Volanesorsen in open label extension period is counted.

Summary of study drug exposure by dose and duration of exposure and by ethnicity for FCS patients treated with volanesorsen is presented in Table 17 and Table 18. A total of 14 hispanic or latino FCS patients were treated with volanesorsen in CS2, CS6, CS16, and CS7 studies. The mean duration of exposure in FCS patients of hispanic or latino ehinicity was 47.23 weeks and there were a total of 12.67 patient-years of exposure to volanesorsen. Whereas in FCS patients of not hispanic or latino ethnicity (78 patients), the mean duration of exposure was 67.22 weeks and there were a total of 100.49 patient-years of exposure to volanesorsen.

**Table 17: Summary of Study Drug Exposure – Safety Set: Patients with Familial Chylomicronemia Syndrome Treated with Volanesorsen from CS2, CS6, CS16, and CS7 by Dose and Duration of Exposure (Hispanic or Latino)**

| Parameter | 300 mg Weekly (N=6)/ Total Patient Year[a]=3.22 | 300 mg Biweekly Post AE/stopping Rule (N=8)/ Total Patient Year[a]=9.45 | 300 mg Biweekly Post W13 Cohort (N=0)/ Total Patient Year[a]=0 | Overall (N=14)/ Total Patient Year[a]=12.67 | Overall Patient Year |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0 - 13 Weeks | 2 (33.3) | 0 | 0 | 2 (14.3) | 0.39 |
| >13 - 26 Weeks | 2 (33.3) | 1 (12.5) | 0 | 3 (21.4) | 1.11 |
| >26 - 52 Weeks | 1 (16.7) | 2 (25.0) | 0 | 3 (21.4) | 2.58 |
| >52 - 78 Weeks | 1 (16.7) | 2 (25.0) | 0 | 3 (21.4) | 3.30 |
| >78 - 104 Weeks | 0 | 3 (37.5) | 0 | 3 (21.4) | 5.29 |
| >104 Weeks | 0 | 0 | 0 | 0 | 0 |
| Number of Administration of Study Drug | | | | | |
| n | 6 | 8 | 0 | 14 | |
| Mean (SD, SE) | 26 (18, 7) | 39 (19, 7) | NC (NC, NC) | 34 (19, 5) | |
| Median (P25, P75) | 19 (13, 47) | 42 (23, 54) | NC (NC, NC) | 32 (18, 50) | |
| Min, Max | 9, 51 | 12, 63 | NC, NC | 9, 63 | |
| Duration of Exposure (Weeks)[b] | | | | | |
| n | 6 | 8 | 0 | 14 | |
| Mean (SD, SE) | 28.02 (20.23, 8.26) | 61.64 (28.66, 10.13) | NC (NC, NC) | 47.23 (29.96, 8.01) | |
| Median (P25, P75) | 20.64 (12.14, 51.14) | 58.43 (41.71, 88.57) | NC (NC, NC) | 46.64 (19.14, 63.71) | |

| Parameter | 300 mg Weekly (N=6)/ Total Patient Year[a]=3.22 | 300 mg Biweekly Post AE/stopping Rule (N=8)/ Total Patient Year[a]=9.45 | 300 mg Biweekly Post W13 Cohort (N=0)/ Total Patient Year[a]=0 | Overall (N=14)/ Total Patient Year[a]=12.67 | Patient Year |
|---|---|---|---|---|---|
| Min, Max | 8.14, 55.43 | 16.71, 99.00 | NC, NC | 8.14, 99.00 | |

Abbreviations: AE = adverse event; NC = not calculated; SD = standard deviation; SE = standard error; W = week
Note: Patients without dose adjustment in the index study but with dose adjustment in CS7 are counted in 300 mg Biweekly post AE/stopping rule cohort. Patients who received biweekly dose since the beginning of CS7 study, and patients who changed to 150 mg weekly dose in CS7 study are also included in 300 mg biweekly post AE/stopping rule cohort.
Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] Duration of Exposure (days) = last volanesorsen dose date - first volanesorsen dose date + 1. Duration of exposure (weeks) = duration of exposure (days)/7.

**Table 18: Summary of Study Drug Exposure – Safety Set: Patients with Familial Chylomicronemia Syndrome Treated with Volanesorsen from CS2, CS6, CS16, and CS7 by Dose and Duration of Exposure (Not Hispanic or Latino)**

| Parameter | 300 mg Weekly (N=34)/ Total Patient Year[a]=29.69 | 300 mg Biweekly Post AE/stopping Rule (N=41)/ Total Patient Year[a]=68.39 | 300 mg Biweekly Post W13 Cohort (N=3)/ Total Patient Year[a]=2.41 | Overall (N=78)/ Total Patient Year[a]=100.49 | Overall Patient Year |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0 - 13 Weeks | 9 (26.5) | 1 (2.4) | 0 | 10 (12.8) | 1.50 |
| >13 - 26 Weeks | 5 (14.7) | 1 (2.4) | 2 (66.7) | 8 (10.3) | 2.93 |
| >26 - 52 Weeks | 10 (29.4) | 6 (14.6) | 0 | 16 (20.5) | 12.94 |
| >52 - 78 Weeks | 2 (5.9) | 8 (19.5) | 1 (33.3) | 11 (14.1) | 13.13 |
| >78 - 104 Weeks | 6 (17.6) | 17 (41.5) | 0 | 23 (29.5) | 43.03 |
| >104 Weeks | 2 (5.9) | 8 (19.5) | 0 | 10 (12.8) | 26.95 |
| Number of Administration of Study Drug | | | | | |
| n | 34 | 41 | 3 | 78 | |
| Mean (SD, SE) | 43 (37, 6) | 51 (25, 4) | 33 (23, 13) | 47 (31, 4) | |
| Median (P25, P75) | 30 (13, 66) | 47 (33, 61) | 23 (17, 59) | 45 (22, 63) | |
| Min, Max | 1, 153 | 10, 123 | 17, 59 | 1, 153 | |
| Duration of Exposure (Weeks)[b] | | | | | |
| n | 34 | 41 | 3 | 78 | |
| Mean (SD, SE) | 45.56 (40.25, 6.90) | 87.04 (37.52, 5.86) | 41.86 (29.82, 17.22) | 67.22 (43.48, 4.92) | |
| Median (P25, P75) | 30.14 (12.14, 67.71) | 92.71 (55.71, 102.57) | 25.14 (24.14, 76.29) | 58.71 (27.14, 102.14) | |

| Parameter | 300 mg Weekly (N=34)/ Total Patient Year[a]=29.69 | 300 mg Biweekly Post AE/stopping Rule (N=41)/ Total Patient Year[a]=68.39 | 300 mg Biweekly Post W13 Cohort (N=3)/ Total Patient Year[a]=2.41 | Overall (N=78)/ Total Patient Year[a]=100.49 | Patient Year |
|---|---|---|---|---|---|
| Min, Max | 0.14, 155.29 | 10.14, 155.14 | 24.14, 76.29 | 0.14, 155.29 | |

Abbreviations: AE = adverse event; SD = standard deviation; SE = standard error; W = week
Note: Patients without dose adjustment in the index study but with dose adjustment in CS7 are counted in 300 mg Biweekly post AE/stopping rule cohort. Patients who received biweekly dose since the beginning of CS7 study, and patients who changed to 150 mg weekly dose in CS7 study are also included in 300 mg biweekly post AE/stopping rule cohort.
Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] Duration of Exposure (days) = last volanesorsen dose date - first volanesorsen dose date + 1. Duration of exposure (weeks) = duration of exposure (days)/7.

Summary of study drug exposure by time interval and by ethnicity for patients treated with volanesorsen in CS17 study is presented in Table 19 and Table 20. The mean duration of exposure in all treated patients of hispanic or latino ehinicity (1 patient) from CS17 study was 51.43 weeks and there were a total of 0.99 patient-years of exposure to volanesorsen. Whereas in all treated patients from CS17 study of not hispanic or latino ethnicity (32 patients), the mean duration of exposure was 47.19 weeks and there were a total of 28.94 patient-years of exposure to volanesorsen.

**Table 19: Summary of Study Drug Exposure – Safety Set: All Treated Volanesorsen Patients from CS17 (Hispanic or Latino)**

| Parameter | 300 mg Weekly (N=1)/ Total Patient Year[a]=0.99 | 300 mg Biweekly (N=0)/ Total Patient Year[a]=0 | Overall (N=1)/ Total Patient Year[a]=0.99 | Overall Patient Year |
|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | |
| 0 - 13 Weeks | 0 | 0 | 0 | 0 |
| >13 - 26 Weeks | 0 | 0 | 0 | 0 |
| >26 - 52 Weeks | 1 (100.0) | 0 | 1 (100.0) | 0.99 |
| >52 Weeks | 0 | 0 | 0 | 0 |
| Number of Administration of Study Drug | | | | |
| n | 1 | 0 | 1 | |
| Mean (SD, SE) | 50 (NC, NC) | NC (NC, NC) | 50 (NC, NC) | |
| Median (P25, P75) | 50 (50, 50) | NC (NC, NC) | 50 (50, 50) | |
| Min, Max | 50, 50 | NC, NC | 50, 50 | |
| Duration of Exposure (Weeks)[b] | | | | |
| n | 1 | 0 | 1 | |
| Mean (SD, SE) | 51.43 (NC, NC) | NC (NC, NC) | 51.43 (NC, NC) | |
| Median (P25, P75) | 51.43 (51.43, 51.43) | NC (NC, NC) | 51.43 (51.43, 51.43) | |
| Min, Max | 51.43, 51.43 | NC, NC | 51.43, 51.43 | |

Abbreviations: NC = not calculated; SD = standard deviation; SE = standard error; W = week

[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[b] CS17 has two treatment period, randomized treatment period (up to Week 52) and open-label extension period (on or after Week 53). In randomized treatment period, if the last dose of volanesorsen is given weekly, exposure duration is the minimum of [(Last Dose Date - First Dose Date + 7) + (Last Dose Date - First Dose Date + 1)] and [Last Dose Date - First Dose Date + 1]. If the last dose of volanesorsen is given biweekly, exposure duration is the minimum of [(Last Dose Date - First Dose Date + 14) + {Last Dose Date - First Dose Date + 1)] and [Last Dose Date - First Dose Date + 1]. In open-label extension period, duration of exposure = Last Dose Date - First Dose Date + 1. The total duration is the summation of the duration in each period. Duration of Exposure (weeks) = Duration of Exposure (days)/7.

**Table 20: Summary of Study Drug Exposure – Safety Set: All Treated Volanesorsen Patients from CS17 (Not Hispanic or Latino)**

| Parameter | 300 mg Weekly (N=23)/ Total Patient Year[a]=16.40 | 300 mg Biweekly (N=9)/ Total Patient Year[a]=12.54 | Overall (N=32)/ Total Patient Year[a]=28.94 | Patient Year |
|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | |
| 0 - 13 Weeks | 4 (17.4) | 0 | 4 (12.5) | 0.32 |
| >13 - 26 Weeks | 4 (17.4) | 0 | 4 (12.5) | 1.45 |
| >26 - 52 Weeks | 8 (34.8) | 3 (33.3) | 11 (34.4) | 8.49 |
| >52 Weeks | 7 (30.4) | 6 (66.7) | 13 (40.6) | 18.68 |
| Number of Administration of Study Drug | | | | |
| n | 23 | 9 | 32 | |
| Mean (SD, SE) | 55 (22, 5) | 52 (25, 8) | 54 (23, 4) | |
| Median (P25, P75) | 53 (43, 71) | 44 (29, 64) | 52 (40, 70) | |
| Min, Max | 8, 112 | 27, 92 | 8, 112 | |
| Duration of Exposure (Weeks)[b] | | | | |
| n | 23 | 9 | 32 | |
| Mean (SD, SE) | 37.20 (24.51, 5.11) | 72.73 (28.06, 9.35) | 47.19 (29.88, 5.28) | |
| Median (P25, P75) | 31.57 (19.14, 57.43) | 64.29 (50.57, 72.29) | 46.57 (25.07, 62.71) | |
| Min, Max | 0.86, 88.43 | 46.86, 123.43 | 0.86, 123.43 | |

Abbreviations: SD = standard deviation; SE = standard error; W = week
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] CS17 has two treatment period, randomized treatment period (up to Week 52) and open-label extension period (on or after Week 53). In randomized treatment period, if the last dose of volanesorsen is given weekly, exposure duration is the minimum of [(Last Dose Date - First Dose Date + 7) + (Last Dose Date - First Dose Date + 1)] and [Last Dose Date - First Dose Date + 1]. If the last dose of volanesorsen is given biweekly, exposure duration is the minimum of [(Last Dose Date - First Dose Date + 14) + {Last Dose Date - First Dose Date + 1)] and [Last Dose Date - First Dose Date + 1]. In open-label extension period, duration of exposure = Last Dose Date - First Dose Date + 1. The total duration is the summation of the duration in each period. Duration of Exposure (weeks) = Duration of Exposure (days)/7.

Summary of study drug exposure by age group in FCS patients from CS2, CS6, CS16, and CS7 studies are presented in Table 21. The mean duration of treatment was shorter in patients above 65 years compared to patients between age group of 18-64 years. The total patient years of exposure in age group 18-64 was 107.94, Age 65 – 74 was 5.06 and Age 75 – 84 was 0.16.

**Table 21: Summary of Study Drug Exposure by Age Group – Safety Set: Patients with Familial Chylomicronemia Syndrome Treated with Volanesorsen from CS2, CS6, CS16, and CS7**

| Parameter | Age 18 - 64 (N=84)/ Total Patient Year[a]=107.94 | Age 65 - 74 (N=7)/ Total Patient Year[a]=5.06 | Age 75 - 84 (N=1)/ Total Patient Year[a]=0.16 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=92)/ Total Patient Year[a]=113.16 |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0-13 Weeks | 9 (10.7) | 2 (28.6) | 1 (100.0) | 0 | 12 (13.0) |
| >13-26 Weeks | 10 (11.9) | 1 (14.3) | 0 | 0 | 11 (12.0) |
| >26-52 Weeks | 17 ( 20.2) | 2 (28.6) | 0 | 0 | 19 (20.7) |
| >52-78 Weeks | 13 ( 15.5) | 1 (14.3) | 0 | 0 | 14 (15.2) |
| >78-104 Weeks | 25 ( 29.8) | 1 (14.3) | 0 | 0 | 26 (28.3) |
| >104 Weeks | 10 ( 11.9) | 0 | 0 | 0 | 10 (10.9) |
| Patient Year by Duration of Exposure | | | | | |
| 0 - 13 Weeks | 1.50 | 0.23 | 0.16 | 0 | 1.89 |
| >13 - 26 Weeks | 3.64 | 0.41 | 0 | 0 | 4.05 |
| >26 - 52 Weeks | 13.67 | 1.85 | 0 | 0 | 15.52 |
| >52 - 78 Weeks | 15.39 | 1.04 | 0 | 0 | 16.43 |
| >78 - 104 Weeks | 46.78 | 1.54 | 0 | 0 | 48.32 |
| >104 Weeks | 26.95 | 0 | 0 | 0 | 26.95 |
| Number of Administration of Study Drug | | | | | |
| n | 84 | 7 | 1 | 0 | 92 |
| Mean (SD, SE) | 46 (30, 3) | 31 (22, 8) | 5 (NC, NC) | NC (NC, NC) | 45 (30, 3) |
| Median (P25, P75) | 45 (22, 62) | 33 (13, 50) | 5 (5, 5) | NC (NC, NC) | 44 (20, 60) |
| Min, Max | 1, 153 | 1, 60 | 5, 5 | NC, NC | 1, 153 |

| Parameter | Age 18 - 64 (N=84)/ Total Patient Year[a]=107.94 | Age 65 - 74 (N=7)/ Total Patient Year[a]=5.06 | Age 75 - 84 (N=1)/ Total Patient Year[a]=0.16 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=92)/ Total Patient Year[a]=113.16 |
|---|---|---|---|---|---|
| Treatment Duration (Weeks)[b] | | | | | |
| n | 84 | 7 | 1 | 0 | 92 |
| Mean (SD, SE) | 67.05 (42.31, 4.62) | 37.73 (27.86, 10.53) | 8.14 (NC, NC) | NC (NC, NC) | 64.18 (42.19, 4.40) |
| Median (P25, P75) | 58.71 (27.64, 101.86) | 46.29 (12.00, 54.14) | 8.14 (8.14, 8.14) | NC (NC, NC) | 55.57 (25.64, 100.71) |
| Min, Max | 0.14, 155.29 | 0.14, 80.29 | 8.14, 8.14 | NC, NC | 0.14, 155.29 |

Abbreviations: NC=not calculated; SD=standard deviation; SE=standard error
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] Duration of Exposure (days) = Last Volanesorsen Dose Date - First Volanesorsen Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. Note: CS6/CS16 Volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].

Summary of study drug exposure from CS2, CS6, CS16, and CS7 studies in FCS male and female patients by age group is presented in Table 22 and Table 23, respectively. The mean treatment duration in FCS male patients was shorter in patients within age group 65 – 74 and 75 – 84 years compared to patients between age group of 18-64 years. The total patient years of exposure in age group 18-64 was 38.97, age 65 – 74 was 1.04 and age 75 – 84 was 0.16. The mean treatment duration in FCS female patients was also shorter in female patients above 65 years compared to patients between age group of 18-64 years. The total patient years of exposure in age group 18-64 was 68.97, age 65 – 74 was 4.02.

**Table 22: Summary of Study Drug Exposure by Age Group – Safety Set: Patients with Familial Chylomicronemia Syndrome Treated with Volanesorsen from CS2, CS6, CS16, and CS7 (Males)**

| Parameter | Age 18 - 64 (N=34)/ Total Patient Year[a]=38.97 | Age 65 - 74 (N=1)/ Total Patient Year[a]=1.04 | Age 75 - 84 (N=1)/ Total Patient Year[a]=0.16 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=36)/ Total Patient Year[a]=40.16 |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0-13 Weeks | 3 (8.8) | 0 | 1 (100.0) | 0 | 4 (11.1) |
| >13-26 Weeks | 5 (14.7) | 0 | 0 | 0 | 5 (13.9) |
| >26-52 Weeks | 11 (32.4) | 0 | 0 | 0 | 11 (30.6) |
| >52-78 Weeks | 5 (14.7) | 1 (100.0) | 0 | 0 | 6 (16.7) |
| >78-104 Weeks | 6 (17.6) | 0 | 0 | 0 | 6 (16.7) |
| >104 Weeks | 4 (11.8) | 0 | 0 | 0 | 4 (11.1) |
| Patient Year by Duration of Exposure | | | | | |
| 0 - 13 Weeks | 0.39 | 0 | 0.16 | 0 | 0.55 |
| >13 - 26 Weeks | 1.86 | 0 | 0 | 0 | 1.86 |
| >26 - 52 Weeks | 8.74 | 0 | 0 | 0 | 8.74 |
| >52 - 78 Weeks | 6.30 | 1.04 | 0 | 0 | 7.34 |
| >78 - 104 Weeks | 11.09 | 0 | 0 | 0 | 11.09 |
| >104 Weeks | 10.59 | 0 | 0 | 0 | 10.59 |
| Number of Administration of Study Drug | | | | | |
| n | 34 | 1 | 1 | 0 | 36 |
| Mean (SD, SE) | 44 (32, 5) | 43 (NC, NC) | 5 (NC, NC) | NC (NC, NC) | 43 (31, 5) |
| Median (P25, P75) | 41 (22, 59) | 43 (43, 43) | 5 (5, 5) | NC (NC, NC) | 40 (22, 55) |
| Min, Max | 1, 153 | 43, 43 | 5, 5 | NC, NC | 1, 153 |
| Duration of Exposure (Weeks)[b] | | | | | |
| n | 34 | 1 | 1 | 0 | 36 |
| Mean (SD, SE) | 59.81 (41.34, 7.09) | 54.14 (NC, NC) | 8.14 (NC, NC) | NC (NC, NC) | 58.21 (41.06, 6.84) |
| Median (P25, P75) | 50.93 (27.14, 88.43) | 54.14 (54.14, 54.14) | 8.14 (8.14, 8.14) | NC (NC, NC) | 50.93 (26.14, 86.79) |

| Parameter | Age 18 - 64 (N=34)/ Total Patient Year[a]=38.97 | Age 65 - 74 (N=1)/ Total Patient Year[a]=1.04 | Age 75 - 84 (N=1)/ Total Patient Year[a]=0.16 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=36)/ Total Patient Year[a]=40.16 |
|---|---|---|---|---|---|
| Min, Max | 0.14, 155.29 | 54.14, 54.14 | 8.14, 8.14 | NC, NC | 0.14, 155.29 |

Abbreviations: NC = not calculated; SD = standard deviation; SE = standard error
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] Duration of Exposure (days) = Last Volanesorsen Dose Date - First Volanesorsen Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. Note: CS6/CS16 Volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].

**Table 23: Summary of Study Drug Exposure by Age Group – Safety Set: Patients with Familial Chylomicronemia Syndrome Treated with Volanesorsen from CS2, CS6, CS16, and CS7 (Females)**

| Parameter | Age 18 - 64 (N=50)/ Total Patient Year[a]=68.97 | Age 65 - 74 (N=6)/ Total Patient Year[a]=4.02 | Age 75 - 84 (N=0)/ Total Patient Year[a]=0 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=56)/ Total Patient Year[a]=73.00 |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0-13 Weeks | 6 (12.0) | 2 (33.3) | 0 | 0 | 8 (14.3) |
| >13-26 Weeks | 5 (10.0) | 1 (16.7) | 0 | 0 | 6 (10.7) |
| >26-52 Weeks | 6 (12.0) | 2 (33.3) | 0 | 0 | 8 (14.3) |
| >52-78 Weeks | 8 (16.0) | 0 | 0 | 0 | 8 (14.3) |
| >78-104 Weeks | 19 (38.0) | 1 (16.7) | 0 | 0 | 20 (35.7) |
| >104 Weeks | 6 (12.0) | 0 | 0 | 0 | 6 (10.7) |
| Patient Year by Duration of Exposure | | | | | |
| 0 - 13 Weeks | 1.11 | 0.23 | 0 | 0 | 1.34 |
| >13 - 26 Weeks | 1.78 | 0.41 | 0 | 0 | 2.19 |
| >26 - 52 Weeks | 4.94 | 1.85 | 0 | 0 | 6.78 |
| >52 - 78 Weeks | 9.09 | 0 | 0 | 0 | 9.09 |
| >78 - 104 Weeks | 35.69 | 1.54 | 0 | 0 | 37.23 |
| >104 Weeks | 16.36 | 0 | 0 | 0 | 16.36 |
| Number of Administration of Study Drug | | | | | |
| n | 50 | 6 | 0 | 0 | 56 |
| Mean (SD, SE) | 48 (29, 4) | 29 (23, 9) | NC (NC, NC) | NC (NC, NC) | 46 (29, 4) |
| Median (P25, P75) | 47 (19, 63) | 25 (13, 50) | NC (NC, NC) | NC (NC, NC) | 46 (19, 61) |

| Parameter | Age 18 - 64 (N=50)/ Total Patient Year[a]=68.97 | Age 65 - 74 (N=6)/ Total Patient Year[a]=4.02 | Age 75 - 84 (N=0)/ Total Patient Year[a]=0 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=56)/ Total Patient Year[a]=73.00 |
|---|---|---|---|---|---|
| Min, Max | 2, 123 | 1, 60 | NC, NC | NC, NC | 1, 123 |
| Duration of exposure (Weeks)[b] | | | | | |
| n | 50 | 6 | 0 | 0 | 56 |
| Mean (SD, SE) | 71.98 (42.66, 6.03) | 35.00 (29.47, 12.03) | NC (NC, NC) | NC (NC, NC) | 68.02 (42.82, 5.72) |
| Median (P25, P75) | 79.14 (41.29, 102.29) | 33.71 (12.00, 50.14) | NC (NC, NC) | NC (NC, NC) | 61.43 (25.14, 102.07) |
| Min, Max | 1.14, 154.86 | 0.14, 80.29 | NC, NC | NC, NC | 0.14, 154.86 |

Abbreviations: FCS = familial chylomicronemia syndrome; NC = not calculated; SD = standard deviation; SE = standard error
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] Duration of Exposure (days) = Last Volanesorsen Dose Date - First Volanesorsen Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. Note: CS6/CS16 Volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].

Summary of study drug exposure by age group for all patients treated with volanesorsen from CS1, CS13, CS2, CS4, CS6, CS7, CS16, and CS17 is presented in Table 24. The mean duration of exposure is shorter in patients within age group 65 – 74 and 75 – 84 years as compared to patients within the age group of 18-64 years. The total patient years of exposure in age group 18-64 was 172.24, age 65 – 74 was 11.72 and age 75 – 84 was 0.39.

**Table 24: Summary of Study Drug Exposure by Age Group – Safety Set: All Treated Volanesorsen Patients from CS1, CS13, CS2, CS4, CS6, CS7, CS16, and CS17**

| Parameter | Age 18 - 64 (N=312)/ Total Patient Year[a]=172.24 | Age 65 - 74 (N=26)/ Total Patient Year[a]=11.72 | Age 75 - 84 (N=2)/ Total Patient Year[a]=0.39 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=340)/ Total Patient Year[a]=184.34 |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0-13 Weeks | 164 (52.6) | 12 (46.2) | 2 (100.0) | 0 | 178 (52.4) |
| >13-26 Weeks | 58 (18.6) | 8 (30.8) | 0 | 0 | 66 (19.4) |
| >26-52 Weeks | 30 (9.6) | 3 (11.5) | 0 | 0 | 33 (9.7) |
| >52-78 Weeks | 22 (7.1) | 2 (7.7) | 0 | 0 | 24 (7.1) |
| >78-104 Weeks | 26 (8.3) | 1 (3.8) | 0 | 0 | 27 (7.9) |
| >104 Weeks | 12 (3.8) | 0 | 0 | 0 | 12 (3.5) |
| Patient Year by Duration of Exposure | | | | | |
| 0 - 13 Weeks | 16.72 | 2.08 | 0.39 | 0 | 19.19 |
| >13 - 26 Weeks | 25.22 | 3.52 | 0 | 0 | 28.74 |
| >26 - 52 Weeks | 23.61 | 2.42 | 0 | 0 | 26.03 |
| >52 - 78 Weeks | 26.69 | 2.15 | 0 | 0 | 28.84 |
| >78 - 104 Weeks | 48.48 | 1.54 | 0 | 0 | 50.02 |
| >104 Weeks | 31.52 | 0 | 0 | 0 | 31.52 |
| Number of Administration of Study Drug | | | | | |
| n | 312 | 26 | 2 | 0 | 340 |
| Mean (SD, SE) | 24 (26, 1) | 23 (19, 4) | 9 (6, 4) | NC (NC, NC) | 24 (25, 1) |
| Median (P25, P75) | 13 (5, 33) | 17 (13, 26) | 9 (5, 13) | NC (NC, NC) | 13 (6, 33) |
| Min, Max | 1, 153 | 1, 81 | 5, 13 | NC, NC | 1, 153 |

| Parameter | Age 18 - 64 (N=312)/ Total Patient Year[a]=172.24 | Age 65 - 74 (N=26)/ Total Patient Year[a]=11.72 | Age 75 - 84 (N=2)/ Total Patient Year[a]=0.39 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=340)/ Total Patient Year[a]=184.34 |
|---|---|---|---|---|---|
| Duration of Exposure (Weeks) | | | | | |
| n | 312 | 26 | 2 | 0 | 340 |
| Mean (SD, SE) | 28.80 (35.86, 2.03) | 23.52 (19.46, 3.82) | 10.14 (2.83, 2.00) | NC (NC, NC) | 28.29 (34.81, 1.89) |
| Median (P25, P75) | 12.29 (3.14, 41.21) | 19.86 (12.00, 25.14) | 10.14 (8.14, 12.14) | NC (NC, NC) | 12.29 (3.14, 37.86) |
| Min, Max | 0.14, 155.29 | 0.14, 80.29 | 8.14, 12.14 | NC, NC | 0.14, 155.29 |

Abbreviations: NC = not calculated; SD = standard deviation; SE = standard error
Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of volanesorsen in open label extension period is counted.

Summary of study drug exposure by age group for all patients treated with volanesorsen from CS1, CS13, CS2, CS4, CS6, CS7, CS16, and CS17 for males and females is presented in Table 25 and Table 26, respectively. The mean duration of exposure was shorter in male patients within age groups 65 – 74 and 75 – 84 as compared to patients within the age group of 18-64 years. The total patient years of exposure in age group 18-64 was 74.14, age 65 – 74 was 4.37 and age 75 – 84 was 0.39. Also, the mean duration of exposure was shorter in female patients above 65 years of age as compared to patients within the age group of 18-64 years. The total patient years of exposure in age group 18-64 was 98.09, age 65 – 74 was 7.35.

**Table 25: Summary of Study Drug Exposure by Age Group – Safety Set: All Treated Volanesorsen Patients from CS1, CS13, CS2, CS4, CS6, CS7, CS16, and CS17 (Males)**

| Parameter | Age 18 - 64 (N=180)/ Total Patient Year[a]=74.14 | Age 65 - 74 (N=11)/ Total Patient Year[a]=4.37 | Age 75 - 84 (N=2)/ Total Patient Year[a]=0.39 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=193)/ Total Patient Year[a]=78.90 |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0-13 Weeks | 102 (56.7) | 4 (36.4) | 2 (100.0) | 0 | 108 (56.0) |
| >13-26 Weeks | 45 (25.0) | 6 (54.5) | 0 | 0 | 51 (26.4) |
| >26-52 Weeks | 16 (8.9) | 0 | 0 | 0 | 16 (8.3) |
| >52-78 Weeks | 7 (3.9) | 1 (9.1) | 0 | 0 | 8 (4.1) |
| >78-104 Weeks | 6 (3.3) | 0 | 0 | 0 | 6 (3.1) |
| >104 Weeks | 4 (2.2) | 0 | 0 | 0 | 4 (2.1) |
| Patient Year by Duration of Exposure | | | | | |
| 0 - 13 Weeks | 11.13 | 0.68 | 0.39 | 0 | 12.20 |
| >13 - 26 Weeks | 20.03 | 2.65 | 0 | 0 | 22.68 |
| >26 - 52 Weeks | 12.46 | 0 | 0 | 0 | 12.46 |
| >52 - 78 Weeks | 8.84 | 1.04 | 0 | 0 | 9.87 |
| >78 - 104 Weeks | 11.09 | 0 | 0 | 0 | 11.09 |
| >104 Weeks | 10.59 | 0 | 0 | 0 | 10.59 |
| Number of Administration of Study Drug | | | | | |
| n | 180 | 11 | 2 | 0 | 193 |
| Mean (SD, SE) | 19 (22, 2) | 19 (10, 3) | 9 (6, 4) | NC (NC, NC) | 19 (21, 2) |
| Median (P25, P75) | 13 (6, 26) | 19 (13, 23) | 9 (5, 13) | NC (NC, NC) | 13 (6, 24) |
| Min, Max | 1, 153 | 1, 43 | 5, 13 | NC, NC | 1, 153 |

| Parameter | Age 18 - 64 (N=180)/ Total Patient Year[a]=74.14 | Age 65 - 74 (N=11)/ Total Patient Year[a]=4.37 | Age 75 - 84 (N=2)/ Total Patient Year[a]=0.39 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=193)/ Total Patient Year[a]=78.90 |
|---|---|---|---|---|---|
| Duration of exposure (Weeks) | | | | | |
| n | 180 | 11 | 2 | 0 | 193 |
| Mean (SD, SE) | 21.49 (28.01, 2.09) | 20.71 (13.59, 4.10) | 10.14 (2.83, 2.00) | NC (NC, NC) | 21.33 (27.24, 1.96) |
| Median (P25, P75) | 12.14 (3.14, 25.14) | 22.14 (12.00, 24.29) | 10.14 (8.14, 12.14) | NC (NC, NC) | 12.14 (3.14, 25.14) |
| Min, Max | 0.14, 155.29 | 0.14, 54.14 | 8.14, 12.14 | NC, NC | 0.14, 155.29 |

Abbreviations: NC = not calculated; SD = standard deviation; SE = standard error

Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].

[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.

[b] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of Volanesorsen in open label extension period is counted.

**Table 26: Summary of Study Drug Exposure by Age Group – Safety Set: All Treated Volanesorsen Patients from CS1, CS13, CS2, CS4, CS6, CS7, CS16, and CS17 (Females)**

| Parameter | Age 18 - 64 (N=132)/ Total Patient Year[a]=98.09 | Age 65 - 74 (N=15)/ Total Patient Year[a]=7.35 | Age 75 - 84 (N=0)/ Total Patient Year[a]=0 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=147)/ Total Patient Year[a]=105.45 |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0-13 Weeks | 62 (47.0) | 8 (53.3) | 0 | 0 | 70 (47.6) |
| >13-26 Weeks | 13 (9.8) | 2 (13.3) | 0 | 0 | 15 (10.2) |
| >26-52 Weeks | 14 (10.6) | 3 (20.0) | 0 | 0 | 17 (11.6) |
| >52-78 Weeks | 15 (11.4) | 1 (6.7) | 0 | 0 | 16 (10.9) |
| >78-104 Weeks | 20 (15.2) | 1 (6.7) | 0 | 0 | 21 (14.3) |
| >104 Weeks | 8 (6.1) | 0 | 0 | 0 | 8 (5.4) |
| Patient Year by Duration of Exposure | | | | | |
| 0 - 13 Weeks | 5.59 | 1.41 | 0 | 0 | 6.99 |
| >13 - 26 Weeks | 5.19 | 0.87 | 0 | 0 | 6.06 |
| >26 - 52 Weeks | 11.15 | 2.42 | 0 | 0 | 13.57 |
| >52 - 78 Weeks | 17.86 | 1.11 | 0 | 0 | 18.97 |
| >78 - 104 Weeks | 37.39 | 1.54 | 0 | 0 | 38.93 |
| >104 Weeks | 20.93 | 0 | 0 | 0 | 20.93 |
| Number of Administration of Study Drug | | | | | |
| n | 132 | 15 | 0 | 0 | 147 |
| Mean (SD, SE) | 30 (30, 3) | 26 (24, 6) | NC (NC, NC) | NC (NC, NC) | 30 (29, 2) |
| Median (P25, P75) | 19 (4, 50) | 15 (13, 50) | NC (NC, NC) | NC (NC, NC) | 18 (5, 50) |
| Min, Max | 1, 123 | 1, 81 | NC, NC | NC, NC | 1, 123 |

| Parameter | Age 18 - 64 (N=132)/ Total Patient Year[a]=98.09 | Age 65 - 74 (N=15)/ Total Patient Year[a]=7.35 | Age 75 - 84 (N=0)/ Total Patient Year[a]=0 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=147)/ Total Patient Year[a]=105.45 |
|---|---|---|---|---|---|
| Duration of exposure (Weeks)[b] | | | | | |
| n | 132 | 15 | 0 | 0 | 147 |
| Mean (SD, SE) | 38.78 (42.51, 3.70) | 25.57 (23.10, 5.97) | NC (NC, NC) | NC (NC, NC) | 37.43 (41.09, 3.39) |
| Median (P25, P75) | 18.64 (2.14, 64.00) | 12.14 (12.00, 46.29) | NC (NC, NC) | NC (NC, NC) | 18.14 (3.14, 59.14) |
| Min, Max | 0.14, 154.86 | 0.14, 80.29 | NC, NC | NC, NC | 0.14, 154.86 |

Abbreviations: NC = not calculated; SD = standard deviation; SE = standard error
Note: CS6/CS16 volanesorsen patients who rolled over to CS7 are counted only once in this table. If the last dose of volanesorsen in CS6/CS16 is given weekly, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 7) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1]. If the last dose of volanesorsen in CS6/CS16 is given every 2 weeks, exposure duration is the minimum of [(Last Dose Date in CS6/CS16 - First Dose Date in CS6/CS16 + 14) + (Last Dose Date in CS7 - First Dose Date in CS7 + 1)] and [Last Dose Date in CS7 - First Dose Date in CS6/CS16 + 1].
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of Volanesorsen in open label extension period is counted.

Summary of study drug exposure by age group for patients treated with volanesorsen in CS17 study is presented in Table 27. The mean duration of exposure was shorter in patients above 65 years of age as compared to patients within the age group of 18-64 years. The total patient years of exposure in age group 18-64 was 28.24, age 65 – 74 was 1.69.

**Table 27 : Summary of Study Drug Exposure by Age Group – Safety Set: All Treated Volanesorsen Patients from CS17**

| Parameter | Age 18 - 64 (N=31)/ Total Patient Year[a]=28.24 | Age 65 - 74 (N=2)/ Total Patient Year[a]=1.69 | Age 75 - 84 (N=0)/ Total Patient Year[a]=0 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=33)/ Total Patient Year[a]=29.93 |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0 - 13 Weeks | 4 (12.9) | 0 | 0 | 0 | 4 (12.1) |
| >13 - 26 Weeks | 4 (12.9) | 0 | 0 | 0 | 4 (12.1) |
| >26 - 52 Weeks | 11 (35.5) | 1 (50.0) | 0 | 0 | 12 (36.4) |
| >52 - 78 Weeks | 9 (29.0) | 1 (50.0) | 0 | 0 | 10 (30.3) |
| >78 - 104 Weeks | 1 (3.2) | 0 | 0 | 0 | 1 (3.0) |
| >104 Weeks | 2 (6.5) | 0 | 0 | 0 | 2 (6.1) |
| Patient Year by Duration of Exposure | | | | | |
| 0 - 13 Weeks | 0.32 | 0 | 0 | 0 | 0.32 |
| >13 - 26 Weeks | 1.45 | 0 | 0 | 0 | 1.45 |
| >26 - 52 Weeks | 8.90 | 0.57 | 0 | 0 | 9.48 |
| >52 - 78 Weeks | 11.30 | 1.11 | 0 | 0 | 12.41 |
| >78 - 104 Weeks | 1.69 | 0 | 0 | 0 | 1.69 |
| >104 Weeks | 4.57 | 0 | 0 | 0 | 4.57 |
| Number of Administration of Study Drug | | | | | |
| n | 31 | 2 | 0 | 0 | 33 |
| Mean (SD, SE) | 53 (22, 4) | 68 (18, 13) | NC (NC, NC) | NC (NC, NC) | 54 (22, 4) |
| Median (P25, P75) | 50 (37, 69) | 68 (55, 81) | NC (NC, NC) | NC (NC, NC) | 50 (43, 69) |
| Min, Max | 8, 112 | 55, 81 | NC, NC | NC, NC | 8, 112 |

| Parameter | Age 18 - 64 (N=31)/ Total Patient Year[a]=28.24 | Age 65 - 74 (N=2)/ Total Patient Year[a]=1.69 | Age 75 - 84 (N=0)/ Total Patient Year[a]=0 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=33)/ Total Patient Year[a]=29.93 |
|---|---|---|---|---|---|
| Duration of Exposure (Weeks)[b] | | | | | |
| n | 31 | 2 | 0 | 0 | 33 |
| Mean (SD, SE) | 47.53 (30.16, 5.42) | 44.07 (19.90, 14.07) | NC (NC, NC) | NC (NC, NC) | 47.32 (29.42, 5.12) |
| Median (P25, P75) | 46.86 (21.14, 64.29) | 44.07 (30.00, 58.14) | NC (NC, NC) | NC (NC, NC) | 46.86 (29.00, 61.14) |
| Min, Max | 0.86, 123.43 | 30.00, 58.14 | NC, NC | NC, NC | 0.86, 123.43 |

Abbreviations: NC = not calculated; SD = standard deviation; SE = standard error
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of Volanesorsen in open label extension period is counted.

Summary of study drug exposure by age group for patients treated with volanesorsen in CS17 study results for males and females is presented in Table 28 and Table 29, respectively. The mean duration of exposure in male patients within the age group of 18-64 years was 37.13. The total patient years of exposure in male patients for age group 18-64 was 7.12. Also, the mean duration of exposure in female patients above 65 years of age was 44.07 which was shorter as compared to female patients within the age group of 18-64 years. The total patient years of exposure in age group 18-64 was 21.12, age 65–74 was 1.69.

**Table 28: Summary of Study Drug Exposure by Age Group – Safety Set: All Treated Volanesorsen Patients from CS17 (Males)**

| Parameter | Age 18 - 64 (N=10)/ Total Patient Year[a]=7.12 | Age 65 - 74 (N=0)/ Total Patient Year[a]=0 | Age 75 - 84 (N=0)/ Total Patient Year[a]=0 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=10)/ Total Patient Year[a]=7.12 |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0 - 13 Weeks | 1 (10.0) | 0 | 0 | 0 | 1 (10.0) |
| >13 - 26 Weeks | 2 (20.0) | 0 | 0 | 0 | 2 (20.0) |
| >26 - 52 Weeks | 5 (50.0) | 0 | 0 | 0 | 5 (50.0) |
| >52 - 78 Weeks | 2 (20.0) | 0 | 0 | 0 | 2 (20.0) |
| >78 - 104 Weeks | 0 | 0 | 0 | 0 | 0 |
| >104 Weeks | 0 | 0 | 0 | 0 | 0 |
| Patient Year by Duration of Exposure | | | | | |
| 0 - 13 Weeks | 0.18 | 0 | 0 | 0 | 0.18 |
| >13 - 26 Weeks | 0.68 | 0 | 0 | 0 | 0.68 |
| >26 - 52 Weeks | 3.72 | 0 | 0 | 0 | 3.72 |
| >52 - 78 Weeks | 2.54 | 0 | 0 | 0 | 2.54 |
| >78 - 104 Weeks | 0 | 0 | 0 | 0 | 0 |

| Parameter | Age 18 - 64 (N=10)/ Total Patient Year[a]=7.12 | Age 65 - 74 (N=0)/ Total Patient Year[a]=0 | Age 75 - 84 (N=0)/ Total Patient Year[a]=0 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=10)/ Total Patient Year[a]=7.12 |
|---|---|---|---|---|---|
| >104 Weeks | 0 | 0 | 0 | 0 | 0 |
| Number of Administration of Study Drug | | | | | |
| n | 10 | 0 | 0 | 0 | 10 |
| Mean (SD, SE) | 48 (21, 7) | NC (NC, NC) | NC (NC, NC) | NC (NC, NC) | 48 (21, 7) |
| Median (P25, P75) | 50 (35, 66) | NC (NC, NC) | NC (NC, NC) | NC (NC, NC) | 50 (35, 66) |
| Min, Max | 8, 76 | NC, NC | NC, NC | NC, NC | 8, 76 |
| Duration of Exposure (Weeks)[b] | | | | | |
| n | 10 | 0 | 0 | 0 | 10 |
| Mean (SD, SE) | 37.13 (19.91, 6.30) | NC (NC, NC) | NC (NC, NC) | NC (NC, NC) | 37.13 (19.91, 6.30) |
| Median (P25, P75) | 36.36 (20.29, 46.29) | NC (NC, NC) | NC (NC, NC) | NC (NC, NC) | 36.36 (20.29, 46.29) |
| Min, Max | 9.29, 71.71 | NC, NC | NC, NC | NC, NC | 9.29, 71.71 |

Abbreviations: NC = not calculated; SD = standard deviation; SE = standard error
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of Volanesorsen in open label extension period is counted.

**Table 29: Summary of Study Drug Exposure by Age Group – Safety Set: All Treated Volanesorsen Patients from CS17 (Females)**

| Parameter | Age 18 - 64 (N=21)/ Total Patient Year[a]=21.12 | Age 65 - 74 (N=2)/ Total Patient Year[a]=1.69 | Age 75 - 84 (N=0)/ Total Patient Year[a]=0 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=23)/ Total Patient Year[a]=22.81 |
|---|---|---|---|---|---|
| Number of Patients with Duration of Exposure - n(%) | | | | | |
| 0 - 13 Weeks | 3 (14.3) | 0 | 0 | 0 | 3 (13.0) |
| >13 - 26 Weeks | 2 (9.5) | 0 | 0 | 0 | 2 (8.7) |
| >26 - 52 Weeks | 6 (28.6) | 1 (50.0) | 0 | 0 | 7 (30.4) |
| >52 - 78 Weeks | 7 (33.3) | 1 (50.0) | 0 | 0 | 8 (34.8) |
| >78 - 104 Weeks | 1 (4.8) | 0 | 0 | 0 | 1 (4.3) |
| >104 Weeks | 2 (9.5) | 0 | 0 | 0 | 2 (8.7) |
| Patient Year by Duration of Exposure | | | | | |
| 0 - 13 Weeks | 0.14 | 0 | 0 | 0 | 0.14 |
| >13 - 26 Weeks | 0.77 | 0 | 0 | 0 | 0.77 |
| >26 - 52 Weeks | 5.18 | 0.57 | 0 | 0 | 5.75 |
| >52 - 78 Weeks | 8.76 | 1.11 | 0 | 0 | 9.88 |
| >78 - 104 Weeks | 1.69 | 0 | 0 | 0 | 1.69 |

| Parameter | Age 18 - 64 (N=21)/ Total Patient Year[a]=21.12 | Age 65 - 74 (N=2)/ Total Patient Year[a]=1.69 | Age 75 - 84 (N=0)/ Total Patient Year[a]=0 | Age 85+ (N=0)/ Total Patient Year[a]=0 | Overall (N=23)/ Total Patient Year[a]=22.81 |
|---|---|---|---|---|---|
| >104 Weeks | 4.57 | 0 | 0 | 0 | 4.57 |
| Number of Administration of Study Drug | | | | | |
| n | 21 | 2 | 0 | 0 | 23 |
| Mean (SD, SE) | 55 (23, 5) | 68 (18, 13) | NC (NC, NC) | NC (NC, NC) | 56 (23, 5) |
| Median (P25, P75) | 50 (43, 71) | 68 (55, 81) | NC (NC, NC) | NC (NC, NC) | 50 (43, 72) |
| Min, Max | 19, 112 | 55, 81 | NC, NC | NC, NC | 19, 112 |
| Duration of Exposure (Weeks)[b] | | | | | |
| n | 21 | 2 | 0 | 0 | 23 |
| Mean (SD, SE) | 52.48 (33.25, 7.26) | 44.07 (19.90, 14.07) | NC (NC, NC) | NC (NC, NC) | 51.75 (32.08, 6.69) |
| Median (P25, P75) | 51.43 (30.43, 70.00) | 44.07 (30.00, 58.14) | NC (NC, NC) | NC (NC, NC) | 51.43 (30.00, 70.00) |
| Min, Max | 0.86, 123.43 | 30.00, 58.14 | NC, NC | NC, NC | 0.86, 123.43 |

Abbreviations: NC = not calculated; SD = standard deviation; SE = standard error
[a] Total Patient Year is the summation of total exposure for each subject under each subgroup or overall, which is the last dose date - first dose date plus 1, divided by 365.25.
[b] Duration of Exposure (days) = Last Dose Date - First Dose Date + 1. Duration of Exposure (weeks) = Duration of Exposure (days)/7. For CS17, patients received Volanesorsen in blinded treatment period will use the same rule as CS6/CS16 to calculate the duration; for patients only received Volanesorsen starting from open label extension period, only exposure after first dosing of volanesorsen in open label extension period is counted.

# PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

## SIV. 1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

**History of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameters**

Reason for exclusion: Volanesorsen has been associated with reductions in platelet count in patients treated in clinical trials and non clinical studies and may result in thrombocytopenia. Patients with history of bleeding diathesis or coagulopathy or clinically-significant abnormality in coagulation parameter were therefore excluded to ensure that they did not confound the safety evaluation of volanesorsen and to ensure that patients were not put at increased risk.

Is it considered to be included as missing information?: No

Rationale: The use of volanesorsen is contraindicated in patients with chronic or unexplained thrombocytopenia. Thrombocytopenia is considered as an important identified risk of volanesorsen.

**Active pancreatitis**

Reason for exclusion: Active pancreatitis within 4 weeks prior to screening was exclusionary, since such patients were deemed too unstable and were therefore excluded to ensure that they did not confound the safety evaluation of volanesorsen.

Is it considered to be included as missing information?: No

Rationale: It is not anticipated that the safety profile of volanesorsen would be different in patients with active pancreatitis as volanesorsen is indicated as an adjunct to diet in adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate.

**Active hepatic injury with ALT/AST > 3 × upper limit of normal (ULN)**

Reason for exclusion: Patients with active hepatic injury with ALT/AST > 3 × ULN were excluded to avoid treatment of patients with active liver disease, as this would interfere with interpretation and assessment of efficacy and safety endpoints in a population who may have an underlying metabolic liver disease.

Is it considered to be included as missing information?: Yes

**Diabetes mellitus with any of the following:**

a. **Newly diagnosed within 12 weeks of Screening**
b. **HbA1c ≥ 9.0% at Screening**
c. **Recent change in anti-diabetic pharmacotherapy (change in dosage or addition of new medication within 12 weeks of Screening [with the exception of ± 10 units of insulin])**
d. **Anticipated need to change dose or type of medication during the treatment period of**

**the study (with the exception of ± 10 units of insulin)**

**e. Current use of GLP-1 agonists.**

Reason for exclusion: Uncontrolled diabetes mellitus was exclusionary to avoid the enrolment of subjects who might have needed new medications during the trial, which would have confounded the safety evaluation of volanesorsen.

Is it considered to be included as missing information?: No

Rationale: It is not anticipated that the safety profile of volanesorsen would be different in patients with uncontrolled diabetes. The safety data to date suggest that volanesorsen has been well-tolerated at dose levels up to 300 mg in patients with high triglycerides (including type 2 diabetes patients and administration in combination with fibrates and statins) with the most common AEs being local to the injection site and predominantly mild.

**Use of any of the following: Statins, omega-3 fatty acids (prescription or over-the-counter [OTC]), or fibrates unless on a stable dose for at least 3 months prior to Screening and dose and regimen expected to remain constant during the treatment period. Patients taking OTC omega-3 fatty acids should make every effort to remain on the same brand throughout the study.**

Reason for exclusion: Exclusion criteria requiring patients to be on stable dose regimen of these medications were adopted either to meet the required medical standards or to allow for an adequate evaluation of the primary and secondary endpoints in the concerned clinical trials.

Is it considered to be included as missing information?: No

Rationale: Such factors were shown not to have a clinically relevant impact on the target population for the proposed indication in the pivotal clinical trial. Therefore, it is not anticipated that the safety profile of volanesorsen would be different in these patients.

## SIV. 2 Limitations to Detect Adverse Reactions Common in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

# SIV. 3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

## Table 30: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

| Type of special population | Exposure |
|---|---|
| Elderly | Across Studies CS2, CS6, CS16 and CS7 (in FCS patients), of the 92 patients enrolled and treated with volanesorsen in these studies, 8 (8.7%) were aged 65 or over, while 84 (91.3%) were younger than 65 years old.<br>Based on the limited data available on the use of volanesorsen in patients aged 65 or over, there is no evidence that elderly patients have a safety or efficacy profile that differs from younger adult patients. No overall differences in safety, PK or effectiveness were observed between patients aged 65 or over and younger patients. |
| Pregnant or breastfeeding women | Not included in the clinical trial development programme. |
| Patients with Hepatic Impairment | Not included in the clinical trial development programme. |
| Patients with Renal Impairment | Specific studies in patients with renal impairment have not been conducted, but population PK analysis suggests that mild (eGFR 60 to 89 mL/min/1.73m$^2$) and moderate (eGFR 30 to 59 mL/min/1.73m$^2$) renal impairment has no clinically relevant effect on the systemic exposure of WAYLIVRA. In this analysis, 7 patients were included in the moderate impairment group, with the lowest eGFR value being 49.5 mL/min/1.73m$^2$. Therefore, no dose adjustment is necessary in patients with mild to moderate renal impairment. No data are available in patients with severe (GFR < 30 mL/min/1.73m$^2$) renal impairment. |
| Patients with Other Relevant Co-morbidity | Overall, 10 patients (15%) in the pivotal trial in patients with FCS and 37 patients (33%) in pooled placebo-controlled Phase 3 studies had a history of diabetes. No specific safety signal has been identified in diabetic patients with or without FCS treated with volanesorsen. |
| Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population | It is not expected that the disease severity in post-marketing use would differ from that studied in clinical trials. |
| Subpopulations Carrying Known and Relevant Polymorphisms | The safety of volanesorsen treatment in subpopulations carrying known and relevant polymorphisms has not been studied due to the rarity of the disease and significant number of mutations in FCS causing genes including *LPL*, *APOC2*, *LMF1*, *APOA5* and *GPIHBP1*. It is not anticipated that the safety of volanesorsen treatment in subpopulations will differ from safety in all treated FCS patients. |
| Patients of Different Racial and/or Ethnic Origin | Based on the population PK analysis, race and/or ethnicity has no clinically relevant effect on volanesorsen exposure. |

Abbreviations: APOA5 = apolipoprotein A5; APOC2= apolipoprotein C2; eGFR=estimated glomerular filtration rate; GFR = glomerular filtration rate; GPIHBP1 = glycosylphosphatidylinositol Anchored High Density Lipoprotein Binding Protein 1; FCS= familial chylomicronemia syndrome; LMF1 = lipase Maturation Factor 1; LPL= lipoprotein lipase PK=pharmacokinetic

# PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

## SV.1 Post-authorisation Experience

### SV.1.1. Post-Marketing Exposure in Launched Countries

Volanesorsen has been authorised for sale in all EEA member states and the United Kingdom (UK). Exposure data is available for Austria, France, Germany, Italy and UK where the product has launched. Table 31 presents the estimated cumulative patient exposure in the launched countries, as of 30 April 2021.

Based on the Summary of Product Characteristics for volanesorsen, the recommended starting dose is 285 mg in 1.5 ml injected subcutaneous once weekly for 3 months. Following 3 months, dose frequency should be reduced to 285 mg every 2 weeks. Therefore, over a 12-month period, the average patient receives 30 doses, which is equivalent to an annual total of 30 pre-filled syringes.

To obtain patient years estimates, the total number of distributed pre-filled syringes of volanesorsen was divided by the average annual total of 30 pre-filled syringes. These estimates are presented in Table 31.

**Table 31 Post marketing exposure for volanesorsen as of 30 April 2021 in Launched[1] Countries**

| Geographic Area | Number Pre-Filled Syringes | Number of Patients on Therapy | Patient years |
|---|---|---|---|
| | Cumulative IBD to 30-Apr-2021 | Cumulative IBD to 30-Apr-2021 | Cumulative IBD to 30-Apr-2021 |
| Austria | 81 | 3 | 2.7 |
| France[2,] | 308 | 12 | 10.3 |
| Germany | 371 | 23 | 12.4 |
| Italy[4] | 254 | 11 | 8.5 |
| UK[3] | 552 | 26 | 18.4 |
| **Total** | **1566** | **75** | **52.2** |

Abbreviations: IBD=International Birth Date

[1] Definition of Launch: Once commercially labelled product is first shipped in country and available for supply. This includes availability for distribution of approved RMP materials, ability to promote, regardless of reimbursement status, and all in-country requirements are met. This does not include product that is available through an early access program.

[2] Of the 12 patients, 1 was previously treated in the ATU programme and as a part of commercial use there is a patient support programme available.

[3] Of the 26 patients, 19 were previously treated in the EAMS programme. Patients received Waylivra® through the EAMS programme pre authorization as well as in the post-authorization and pre-launch phase.

[4] Of the 11 patients, 7 patients were treated through an early access programme in the post-authorization and pre-launch phase

### SV.1.2. Exposure for Early Access in Countries in the Post-Authorization and Pre-Launch Phase

Since the approval of Waylivra® on 03 May 2019, patients in France, UK, Spain, the Netherlands, Sweden, Greece and Italy have been treated in early access programs prior to Waylivra® being launched.

As of 30 April 2021, patients in Spain, the Netherlands, Sweden, and Greece continue to be treated through early access prior to Waylivra® being launched. Table 32 presents the estimated cumulative patient exposure for patients in the post-authorization and pre-launch phase.

**Table 32 Exposure from Early Access in Post-Authorization and Pre-launch Phase Countries (as of 30 April 2021)**

| Country | Cumulative Patients in this Phase as of DLP 30 April 2021 |
|---|---|
| Netherlands | 2* |
| Sweden | 2* |
| Greece | 5 |
| Italy | 7** |
| Spain | 16* |
| UK | 19** |
| **Total** | **51** |

*All patients in this phase for the UK, Spain, Sweden and the Netherlands reflect patients previously treated in the respective pre-authorization early access programme or EAMS.
**UK and Italy have now completed this phase and are launched.

### SV.1.3. Cumulative exposure from Pre-Authorisation Early Access Programmes

As of 02 May 2021, 71 patients have been treated with volanesorsen in pre-authorisation early access programmes. This includes access routes with solicited reporting as per ICH E2D: the US Expanded Access Program (EAP), UK Early Access to Medicines Scheme (EAMS), named patient supply in Colombia and Argentina and the French Temporary Authorization for Use (ATU). Additionally, through the Canadian Special Access Program (SAP) and in the Netherlands, Spain, and Sweden with spontaneous reporting.

Pre-authorization access is ongoing in the US (EAP), Colombia, Argentina, and Canada. A cumulative tabulation of demographic information for these programmes can be found in Table 34.

The cumulative exposure for patients treated in these pre-authorization programmes is presented by country in Table 33 below:

## Table 33 Cumulative Exposure from Early Access Programmes (Pre-Authorization)

| Country (Programme Name) | Cumulative Total Patients Treated in the Programme as of 02 May 2021 |
|---|---|
| **Ongoing Programmes** | |
| Canada | 19 |
| US | 9 |
| Colombia | 1 |
| Argentina | 1 |
| **Patients that have transitioned from pre-authorisation to post-authorisation pre-launch phase** | |
| Sweden | 2 |
| Netherlands | 2 |
| Spain | 14 |
| UK (EAMS) | 22 |
| France (ATU) | 1 |
| **Total Patients Treated Across all Programmes** | 71 |

## Table 34: Additional Demographics Information for Early Access Programmes (Pre-Authorization)*

| Source | Sex | | Age (years) | | | Dose | | Dosing Frequency | | | Country | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Male | Female | 18 to 64 | 65+ | Not available | 285 mg | Not available | Weekly | Bi-weekly | Not available | Argentina | Canada | Colombia | France | Netherlands | Spain | Sweden | UK | US |
| **ATU** | 0 | 1 | 1 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| **EAMS** | 8 | 14 | 19 | 2 | 1 | 22 | 0 | 0 | 22 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 22 | 0 |
| **Early Access Programmes** | 20 | 28 | 45 | 3 | 0 | 46 | 2 | 5 | 38 | 5 | 1 | 19 | 1 | 0 | 2 | 14 | 2 | 0 | 9 |
| **Total** | 28 | 43 | 65 | 5 | 1 | 69 | 2 | 5 | 61 | 5 | 1 | 19 | 1 | 1 | 2 | 14 | 2 | 22 | 9 |

ATU=A French Temporary Authorization for Use; EAMS=Early Access to Medicines Scheme; UK=United Kingdom; US=United States
*Please note the following:
1. The age of patients and full date of birth is not collected in EAMS. Therefore, the age has been calculated off year of birth with the assumption of a full year as of 01-Jan-2020.
2. For Canadian sites in the SAP the dose and dosing frequency was estimated as biweekly 285 mg for all patients.
3. Early Access Programmes in pre-authorization phase include patients in Spain, US, Sweden, Canada, Netherlands, Colombia, and Argentina

# PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

## SVI. 1 Potential for Misuse for Illegal Purposes

Volanesorsen is not known to have attributes that make it a candidate for intentional overdose, abuse, or illegal use. Therefore, no potential for misuse for illegal purposes is anticipated.

# PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

## SVII. 1 Identification of Safety Concerns in the Initial RMP Submission

### SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

**Reason for not including an identified or potential risk in the list of safety concerns in the RMP:**

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)

- Constitutional Symptoms (flu-like symptoms, headache, fatigue, arthralgia, myalgia)

In Study CS6, flu-like reactions occurred following 0.1% of volanesorsen injections in patients with FCS. Two patients in the volanesorsen group had 1 event each of influenza-like illness. In CS7 (as of 31 December 2017), 194 events considered related to constitutional symptoms were experienced. The most common AEs were arthralgia (18%), pyrexia (15%), fatigue, (12%), asthenia (10%), chills (10%), and myalgia (10%). The majority of reported AEs were mild with the exception of 2 events of arthralgia, 2 events of chills, and singular events each of arthritis, musculoskeletal pain, myalgia, peripheral arthritis, asthenia, and pain.

Both events of flu-like reaction in Study CS6 were mild. In CS7 (as of 31 December 2017), constitutional symptoms reported as SAEs were influenza-like illness (1) and myalgia (1). Both SAEs were assessed by the reporters as unrelated to volanesorsen.

The flu-like reactions observed represent isolated events therefore, the overall clinical impact of these constitutional symptoms is considered low.

Constitutional symptoms such as fever, chills, and myalgia are commonly observed side effects after systemic administration of phosphorothioate oligonucleotides. Overall 4 (3%) volanesorsen-treated patients across the Phase 2 and 3 Studies (300 mg volanesorsen) developed these symptoms, an incidence much lower than what has been previously seen with mipomersen, where 30% of patients developed flu-like symptoms following injection.

A targeted questionnaire for constitutional symptoms will be utilised to further characterise the nature and incidence of this identified risk during postmarketing experience.

Other reasons for considering the risks not important:

- Potential for Transmission of Infectious Agents

No animal- or human-derived components are used in the manufacture of volanesorsen.

- Potential for Harm from Overdose

There is no clinical experience with overdose of volanesorsen. In clinical studies, the maximal dose of volanesorsen given was 400 mg doses q2d for 1 week, with no immediate safety concerns. Single supratherapeutic IV doses of 300 mg, corresponding to an approximately 4.1 fold increase in volanesorsen $C_{max}$ compared with the value observed after the 300-mg subcutaneous injection, were safe and well tolerated in healthy subjects. No clinical data are

available for doses exceeding these values. In case of overdosage, patients should be carefully observed and supportive care administered, as appropriate. Haemodialysis is unlikely to be beneficial given that WAYLIVRA resides intracellularly or is rapidly distributed into cells.

Accidental overdosing during patient self-administration or administration by a caregiver or healthcare worker is unlikely due to use of single dose pre-filled syringes. If the patient is capable and willing to self-administer the drug, the likelihood of accidental overdose is limited by the way the product is supplied as a pre-filled syringe.

- Potential for Medication Errors

The risk of medication errors in dosing the correct prescribed amount of volanesorsen is considered to be low since volanesorsen is delivered in single use syringes and patients will be instructed on proper subcutaneous administration of the product. The first administered dose of volanesorsen by the patient or care giver will be performed under the instruction/observation of a healthcare provider to support subsequent appropriate use at home.

Failure of the single-use pre-filled syringe is unlikely to occur due to its standard design. Unlike a multi-dose device, the pre-filled and single-use syringe wouldn't deliver more than the planned dose.

- Potential for Off-label Use

Volanesorsen is intended for adult patients with FCS and is not intended for treatment of patients with hypertriglyceridemic disorders of other aetiologies. It is recommended that treatment with volanesorsen should be initiated and remain under the supervision of a physician experienced in the treatment of FCS patients. Expected use in speciality practices plus healthcare provider education, and routine post-marketing surveillance, will reduce any opportunities for off-label use.

### SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risks

- Thrombocytopenia

Thrombocytopenia is listed as an important identified risk in patients with FCS treated with volanesorsen due to incidence versus placebo (75% versus 24%) and occurrence of severe thrombocytopenia ($<50 \times 10^9$/L: 9% 3/33) in pivotal study CS6 with risk for serious bleeding.

Risk-benefit impact: If thrombocytopenia is not recognised and managed appropriately, it can result in bleeding, which in turn can be life-threatening. As a consequence, thrombocytopenia, is considered to be an important identified risk for volanesorsen.

- Injection site reactions

In the pivotal FCS Phase 3 study (CS6), AEs at the injection site were commonly reported in the volanesorsen group. In the volanesorsen group, 76%, 46%, and 24% of patients experienced injection site erythema, injection site pain, and injection site pruritus, respectively, compared to 3%, 9%, and 0% of patients in the placebo group.

Risk-benefit impact: Although adverse reactions are self-limiting, they may lead to non-adherence to the treatment regimen or discontinuation of treatment. As a consequence, injection site reactions are considered to be an important identified risk for WAYLIVRA.

Important Potential Risks

- Immunogenicity

Of the 33 volanesorsen-treated patients in Study CS6, 10 (30%) patients tested positive for anti-drug antibodies (ADA) at some point during the study.

Risk-benefit impact: Anaphylactic reactions and serum sickness can be life-threatening events. Other allergic manifestations involving the skin (erythema, urticaria, wheals, rash) can be mild to severe in intensity. Management of these reactions may require treatment with antihistamines and steroids and have been fully reversible.

- Hepatotoxicity

Adverse events related to hepatoxicity were reported at low frequencies in the Phase 2 and 3 studies (pooled data). A total of 4 (0.1%) volanesorsen-treated patients experienced hepatic enzyme increased, 3 (0.1%) experienced ALT increased, and 2 (0.1%) each experienced AST increased and transaminases increased. Adverse events within the hepatobiliary disorders SOC were reported in 10 (0.2%) of 146 volanesorsen-treated patients in the Phase 2 and 3 studies.

Risk-benefit impact: If not managed appropriately, hepatotoxicity can result in hospitalisation and can be life-threatening. As a consequence, hepatotoxicity is considered to be an important potential risk for volanesorsen.

- Nephrotoxicity

As of 06 January 2017, 2 (6%) volanesorsen-treated patients in Study CS6 and 9 (12%) volanesorsen-treated patients in Study CS16 experienced an AE within the Renal and Urinary Disorders SOC. During the on-study period, 12 (8%) volanesorsen-treated patients and 3 (3%) placebo patients experienced a serum creatinine value ≥ 0.3 mg/dL increase from baseline at any point; 2 (1%) volanesorsen patients and 0 placebo patients experienced a change of this magnitude at the final visit.

Risk-benefit impact: If not managed appropriately, nephrotoxicity can result in hospitalisation and can be life-threatening. As a consequence, nephrotoxicity, is considered to be an important potential risk for WAYLIVRA.

Missing information

- Use in pregnancy and lactation

Risk-benefit impact: There are no data on the use of volanesorsen in pregnant women. Non-clinical studies did not indicate direct or indirect harmful effects with respect to reproductive toxicity.

In non-clinical studies, levels of volanesorsen in milk were very low in lactating mice. Available pharmacodynamic/toxicological data in animals have shown excretion of very low amounts of volanesorsen in milk. Due to the poor oral bioavailability of this medicinal product, it is considered unlikely that these low milk concentrations would result in systemic exposure from

nursing. It is unknown whether volanesorsen or metabolites are excreted in human milk. A risk to the newborn infant therefore cannot be excluded and use during lactation is therefore considered missing information.

- Use in patients with hepatic impairment

Risk-benefit impact: The pharmacokinetics of volanesorsen in patients with hepatic impairment is unknown. Data collection in patients with hepatic impairment is therefore considered warranted and use in this patient population is considered missing information.

- Use in patients with severe renal impairment

Risk-benefit impact: A population pharmacokinetic analysis 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. Data collection in patients with renal impairment is therefore considered warranted and use in this patient population is considered missing information.

- Long-term safety

Risk-benefit impact: Use of volanesorsen has not been assessed in patients for long periods of time. The long-term safety of volanesorsen is therefore unknown and is considered missing information.

- Use in elderly

Risk-benefit impact: Clinical studies included 4 patients with FCS aged 65 treated with volanesorsen in randomised control studies (phase 2 study CS2, 1 patient; CS6, 3 patients), and 6 patients aged 65 and over in the open-label extension study (CS7). No overall differences in safety or effectiveness were observed between these patients and younger patients, however data are limited in this subpopulation. Use in elderly is therefore considered missing information.

## SVII. 2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

There are no new safety concerns and reclassification with a submission of an updated RMP.

## SVII. 3 Details of Important Identified and Potential Risks and Missing Information

### SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

| **Important Identified Risk – Thrombocytopenia** | |
|---|---|
| Potential mechanisms: | No definitive causative mechanism for the platelet reductions observed during treatment with volanesorsen has been identified despite comprehensive investigations having been performed.<br>The investigations have included the following potential causes:<br>Decreased Platelet Production |

| **Important Identified Risk – Thrombocytopenia** | |
|---|---|
| | • Bone marrow biopsies obtained in patients with platelet counts < 50 × $10^9$/L have shown no evidence of an effect of volanesorsen on megakaryocytes.<br><u>Accelerated Platelet Destruction</u><br>• Assessment of antibodies against platelet factor 4 (PF4) did not detect IgG anti-PF4 antibodies, excluding a classical heparin-induced thrombocytopenia like mechanism.<br>• Antiplatelet antibodies and/or Immunoglobulin M anti-PF4 antibodies (detected as a complex between PF4 and polyvinylsulfonate) were detected in a minority of tested patients with thrombocytopenia, including 2 of the patients with Grade 4 thrombocytopenia. All patients in the CS6 clinical trial received heparin on 2 occasions as part of a procedure for measuring lipoprotein lipase activity and this may be an important contributor to the IgM anti-PF4 antibodies. However, the antibodies were seen in both volanesorsen and placebo treated patients and were also seen in some patients prior to dosing with volanesorsen. Therefore, it is unlikely that these antibodies are a significant general cause of the observed platelet count reductions.<br>• Investigations have shown no evidence of thrombotic microangiopathy, disseminated intravascular coagulation, or thrombotic thrombocytopenic purpura.<br>• Normally, about one-third of the platelet mass is pooled in the spleen, where it is in equilibrium with circulating platelets. Splenic pooling of platelets can be increased to 90% in cases of extreme splenomegaly, although total platelet mass and overall platelet survival may remain relatively normal. Gaucher's disease (hereditary lipid storage disease with intracellular lipid accumulation in lysosomes) is an example of a disease with splenomegaly and thrombocytopenia due to platelet pooling in the spleen. Patients with FCS often have an enlarged liver and spleen. The organomegaly results from TG uptake by macrophages, which become foam cells and increase liver or spleen size. In FCS patients, a small inverse correlation was found in all patients between baseline spleen (but not liver) size and baseline platelet count and between change from baseline in spleen size and change from baseline in platelet count in volanesorsen-treated patients only (Studies CS6 and CS16). It is possible that treatment with volanesorsen could increase pooling or clearance of platelets in the spleen and thereby contribute to the development of thrombocytopenia in FCS patients.<br><u>Platelet Function</u><br>• There is no evidence of an effect on platelet function as demonstrated by platelet aggregation studies in monkeys in which no effect on platelet aggregation was seen even at human equivalent doses of volanesorsen that were 2.5-fold higher than the 300 mg/week human therapeutic dose and studies with other ASOs of the same chemical class as volanesorsen. This is supported by lack of any clinically important bleeding events in patients treated with volanesorsen, including the 2 patients with platelet counts < 25 × $10^9$/L.<br><u>Disease Factors</u><br>• A review of recently available natural history data in 87 patients from 3 Canadian clinics within the SMASH registry that was presented at the European Atherosclerosis Society congress (Gaudet et al. 2016) and published in the Journal of Clinical Lipidology (Gaudet et al. 2017) has revealed that FCS patients have a variable platelet count over time, a mean of 11 years, and many FCS patients experience significant thrombocytopenia (as well as thrombocytosis) as part of the natural history of the disease. The |

| **Important Identified Risk – Thrombocytopenia** | |
|---|---|
| | majority (55%) of FCS patients exhibited thrombocytopenia on one or more occasions when followed over prolonged periods of time, including up to 17% exhibiting values < $100 \times 10^9$/L, and some as low as < $50 \times 10^9$/L. In addition, 12% of FCS patients exhibited thrombocytosis (> $450 \times 10^9$/L).<br>Variability was also noted in Study CS6, with 10 placebo patients over the course of the study dropping below the lower limit of normal on at least 1 occasion. However, no placebo patients had values < $100 \times 10^9$/L during the 12-month period of observation in study CS6.<br>Therefore, patients with FCS appear to be at increased risk of thrombocytopenia, and to a lesser degree of thrombocytosis, based on both of these observational datasets. To what degree the significant splenomegaly found in these patients plays a role in platelet variability is unknown.<br>• Some cytokine abnormalities detected at baseline have been implicated in the pathophysiology of various autoimmune diseases and may indicate FCS patients have an underlying immune dysregulation that may be a contributing factor in the antibodies detected.<br><u>Body Weight</u><br>• Body weight was assessed for correlation with a number of PK and PD parameters. Correlations were confirmed statistically between body weight and exposure as indicated by steady-state AUC, where steady-state AUC increased as body weight decreased. Correlations were also confirmed between body weight and percent platelet count decrease, suggesting that patients with lower weights may have an increased overall risk of platelet reductions. Finally, maximum triglyceride reduction was achieved across the body weights suggesting maximum pharmacology ($E_{max}$) was achieved at 300 mg/week independent of body weight.<br>In summary, the results of the investigation have failed to find one single underlying cause and the aetiology of the observed platelet declines appears to be complex. |
| Evidence source(s) and strength of evidence: | Clinical Studies: CS2, CS6, CS7, CS16<br>CS6 and CS16 are the randomised controlled trials.<br>In the non-clinical study, dose and time-dependent reductions in mean platelet count were observed in monkeys, both in the 3-month (40 mg/kg/wk) and 9-month studies (6 mg/kg/wk). |
| Characterisation of the risk: | <u>MedDRA search criteria:</u> SMQs: Haematopoietic thrombocytopenia (broad and narrow), Haemorrhages (excluding laboratory terms) (narrow)<br><u>Frequency</u><br>In the pivotal Phase 3 study (CS6), the total AEs under the category of thrombocytopenia were observed in 23 (69.7%) patients treated with volanesorsen and 3 (9.1%) patients receiving placebo. The most commonly reported events in this category were platelet count decreased observed in 11 (33.3%) patients treated with volanesorsen compared with 1 (3.0%) patients who received placebo, injection site bruising and epistaxis, each in 5 (15.2%) patients treated with volanesorsen compared with no patients who received placebo. Other commonly reported AEs in this category were thrombocytopenia and petechiae each observed in 4 (12.1%) patients treated with volanesorsen compared with no patients who received placebo and injection site haematoma and vaginal haemorrhage each in 2 (6.1%) patients treated with volanesorsen compared with no patients who received placebo.<br>Confirmed (2 consecutive measurements) nadir platelet counts to below normal ($140 \times 10^9$/L) were observed in 68% patients treated with volanesorsen and 13% |

| **Important Identified Risk – Thrombocytopenia** | |
|---|---|
| | placebo patients; confirmed (2 or more consecutive measurements) nadir values to below $100 \times 10^9$/L were observed in 39% patients treated with volanesorsen compared with no patients who received placebo; confirmed nadir values to below $50 \times 10^9$/L were observed in 3 (9.4%) patients treated with volanesorsen compared with no patients who received placebo.<br>Across studies CS2, CS6, CS16 and CS7, a total of 65 (70.7%) patients had 199 events in the category of thrombocytopenia. The most commonly reported events in this category were platelet count decreased in 26 (28.3%) patients, thrombocytopenia in 20 (21.7%) patients, injection site bruising in 13 (14.1%) patients, and epistaxis in 10 (10.9%) patients, injection site haematoma in 8 (8.7%) patients, injection site haemorrhage and ecchymosis each in 6 (6.5%) patients, hematoma and contusion each in 5 (5.4%) patients, haemorrhage and petechiae each in 4 (4.3%) patients. A total of 151 events in 53 (57.6%) patients were considered related to volanesorsen.<br>In Study CS17 (non-FCS patients), the total of 54 AEs under the category of thrombocytopenia were observed in 17 (51.5%) patients treated with volanesorsen. Forty one (41) of these AEs were related to volanesorsen in 16 (48.5%) patients.<br>Across studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, a total of 139 (40.9%) patients had 395 AEs in the category of thrombocytopenia. Two hundred ninety three (293) of these AEs were related to volanesorsen in 107 (31.5%) patients.<br><u>Seriousness/outcomes</u><br>In the pivotal Phase 3 study (CS6), 2 serious adverse events (SAEs) of severe thrombocytopenia were reported. Two (6.1%) FCS patients had thrombocytopenia with platelet counts $< 25 \times 10^9$/L, which led to study treatment discontinuation. Neither of these patients had major bleeding events and both recovered to normal platelet count following drug discontinuation and administration of corticosteroids. One of the 2 patients had a bone marrow biopsy which was normal.<br>Across studies CS2, CS6, CS16 and CS7, 6 (6.5%) patients had SAEs of thrombocytopenia. These were assessed as related to study drug and led to treatment discontinuation. In all these cases, SAEs of thrombocytopenia were resolved following drug discontinuation and/or administration of corticosteroids.<br>In Study CS17 (non FCS patients), there were no serious AEs reported under this category. One (1) AE of platelet count decreased lead to treatment discontinuation. Of the total 54 non-serious AEs reported in 17 (51.5%) patients under this category, 50 AEs were resolved in 13 (39.4%) patients.<br><u>Severity and nature of risk</u><br>In Study CS6, 61 events in the thrombocytopenia category were reported in 23 (69.7%) patients in the volanesorsen group and 3 events were reported in 3 (9.1%) patients in the placebo group. Overall, 20 (24.3%) of the 61 events in this category were reported at the injection site. These effects are concentration dependent and it is possible that the high local tissue concentrations at the injection site following subcutaneous administration could cause a localised and transient disruption of the contact pathway resulting in minor bleeding events such as bruising and injection site bleeding.<br>There were no major bleeding events observed. The most commonly reported bleeding events in the volanesorsen group (excluding the injection site events and laboratory abnormalities) were epistaxis in 5 (15.2%) patients and petechiae in 4 (12.1%) patients; none of the patients in the placebo group experienced these events. The only other bleeding event reported in more than 1 patient in the |

| **Important Identified Risk – Thrombocytopenia** | |
|---|---|
| | volanesorsen group was vaginal haemorrhage reported in 2 (6.1%) patients. All bleeding events were mild; none were reported as SAEs and none led to treatment discontinuation.<br>A review of bleeding events encompassing patients in Studies CS6 and CS16 who experienced bleeding events, their study treatment allocation, their platelet counts immediately before and after the event, and the concomitant medications ongoing at the time of the event, shows that the use of antiplatelet agents or anticoagulants does not appear to increase the risk of bleeding events in patients treated with volanesorsen.<br>Across studies CS2, CS6, CS16 and CS7, of the 6 AEs of thrombocytopenia, 5 AEs in 5 (5.4%) patients were severe and 1 AE in 1 (1.1%) patient was mild in severity. The most commonly reported bleeding events (excluding the injection site events and laboratory abnormalities) were epistaxis in 10 (10.9%) patients, ecchymosis in 6 (6.5%) patients, haematoma and contusion each in 5 (5.4%) patients, haemorrhage and petechiae each in 4 (4.3%) patients, rectal haemorrhage, conjunctival haemorrhage, gingival bleeding, haematuria, mouth haemorrhage and vaginal haemorrhage each in 2 (2.2%) patients. These AEs were generally mild in severity in 45 (48.9%) patients, moderate in severity in 14 (15.2%) patients and 6 (6.5%) of the patients experienced severe AEs under this category. Sixteen (16) of the AEs under this category resulted in permanent discontinuation of volanesorsen in 16 (17.4%) patients.<br>In CS17 (non FCS patients), all AEs in the category of thrombocytopenia were mild in severity in 14 (42.4%) patients. |
| Risk factors and risk groups: | Patients with moderate or severe thrombocytopenia (< $100 \times 10^9$/L). |
| Preventability: | Avoidance of use in patients with chronic and unexplained thrombocytopenia. Platelets should be monitored every 2 weeks during treatment and daily following discontinuation of treatment. Recommendations for adjustments to monitoring frequency and volanesorsen dosing are specified in Table 1 (section 4.2) of the SmPC.<br>Educating healthcare professionals, caregivers and patients of the signs and symptoms of the risk through use of health care provider guide and Patient/Carer Guide. |
| Impact on the risk-benefit balance of the product: | Thrombocytopenia, if not recognised and mitigated, can result in bleeding, which has the potential of being life-threatening. |
| Public health impact: | Based on the prevalence of FCS and the low incidence of severe platelet declines in the safety database, the potential for significant public health impact is low. Non-serious bleeding did occur in FCS patients with declines in platelet counts. However, medical care was not required for these events. |

Abbreviations: AE = adverse event; ASO = antisense oligonucleotide; AUC = area under the curve; FCS = familial chylomicronemia syndrome; IgG = immunoglobulin G; IgM = immunoglobulin M; MedDRA = Medical Dictionary for Regulatory Activities; PF4 = platelet factor 4; PD = pharmacodynamic; PK = pharmacokinetic; SmPC = Summary of Product Characteristics; SMQ =; Standardised MedDRA Query; TG = triglyceride

| **Important Identified Risk – Injection site reactions** | |
|---|---|
| Potential mechanisms: | WAYLIVRA is administered via the subcutaneous route of administration; therefore, injection site reactions may occur. |

| **Important Identified Risk – Injection site reactions** | |
|---|---|
| Evidence source(s) and strength of evidence: | Clinical Studies: CS2, CS6, CS16, CS7<br>CS6 and CS16 are randomised controlled trials.<br>In non-clinical studies, mononuclear cell infiltrates at the subcutaneous injection site were observed in mice, rats, and monkeys. |
| Characterisation of the risk: | MedDRA search criteria: HLT: Injection site reactions<br>SMQ: Extravasation events (injections, infusions and implants) (broad and narrow)<br>Frequency<br>In the pivotal FCS Phase 3 study (CS6), AEs at the injection site were commonly reported in the volanesorsen group. In the volanesorsen group, 75.8%, 45.5%, and 24.2% of patients experienced injection site erythema, injection site pain, and injection site pruritus, respectively, compared to 3%, 9.1%, and 0% of patients in the placebo group.<br>In Study CS7, 42 subjects reported 61.8% of injection site reactions. Of the 42 subjects who reported at least 1 injection site reaction during the study, 33 subjects were treatment naive (64.7%), 8 subjects (57.1%) were from CS6 (volanesorsen), and one subject (33.3%) was from CS16 (volanesorsen). The majority of the injection site reactions (50%) reported by 34 subjects for all treatment groups occurred during the first 13 weeks of study drug treatment. The remaining 50% of injection site reactions were in 16 subjects (23.9%) and occurred from > 13 to 26 weeks of study drug treatment, in 11 subjects (17.2%) during > 26 to 52 weeks of study drug treatment, and in 9 subjects (16.7%) after 52 weeks of study drug treatment.<br>In CS7, fifty five (81%) volanesorsen-treated patients experienced at least 1 local cutaneous reaction at injection site (LCRIS) during the study (based on the revised LCRIS criteria). The most common LCRIS AE was injection site erythema, which occurred in 41 (60%) patients. LCRIS AEs of injection site swelling occurred in 18 (27%) patients, injection site pain occurred in 17 (25%) patients, injection site pruritus and injection site discolouration occurred in 14 (21%) patients each, and injection site induration occurred in 13 (19%) patients. Mean duration to resolution was 193 days.<br>Across studies CS2, CS6, CS16 and CS7, a total of 82 (89.1%) volanesorsen treated patients had 2443 events in the category of injection site reactions. The most commonly reported events in this category were injection site erythema in 70 (76.1%) patients, injection site pain in 43 (46.7%) patients, injection site swelling in 26 (28.3%) patients, injection site discolouration and injection site induration each in 25 (27.2%) patients, injection site pruritus in 24 (26.1%) patients, injection site bruising in 13 (14.1%) patients, injection site oedema in 12 (13%) patients, injection site reaction in 9 (9.8%) patients, injection site hematoma in 8 (8.7%), injection site warmth in 7 (7.6%) patients, injection site haemorrhage and injection site hypoaesthesia in 6 (6.5%) patients each, injection site inflammation and injection site dryness 4 (4.3%) patients each.<br>In CS17 (non-FCS patients), a total of 352 AEs in the category of injection site reaction were reported in 29 (87.9%) patients. One (1) AE reported under this category resulted in treatment discontinuation in 1 (3%) patients. Three forty nine (349) AEs reported under this category were related to volanesorsen in 28 (84.8%) patients.<br>Across studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, a total of 286 (84.1%) patients had 5499 events in the category of injection site reactions. Five |

| **Important Identified Risk – Injection site reactions** | |
|---|---|
| | thousand four hundred and seventy two (5472) of these AEs were related to volanesorsen in 283 (83.2%) patients.<br><u>Seriousness/outcomes</u><br>None of the AEs at the injection site in the Phase 2 and 3 studies and CS7 were considered serious, and there was only 1 severe AE of injection site pain (Study CS7), including no reports of necrosis, abscess, ulceration, or giant cell reactions.<br>Across CS2, CS6, CS16 and CS7, only 2 (2.2%) patients discontinued volanesorsen due to AEs under the category of injection site reactions.<br>In CS17 (non-FCS patients), none of the AEs reported under this category were serious. Of the total 352 AEs in 29 (87.9%) patients, majority of the AEs (341) were resolved in 20 (60.6%) patients.<br>Across studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, none of the AEs reported under this category were serious. Of the total 5499 AEs in 286 (84.1%) patients, the majority of the AEs (5094) reported under this category were resolved in 196 (57.6) patients and 39 AEs led to treatment discontinuation in 15 (4.4%) patients.<br><u>Severity and nature of risk</u><br>The majority of AEs at the injection site were transient (less than 2 days in duration), and were mild and self-limited, requiring no treatment.<br>In CS17 (non-FCS patients), of the total 352 AEs in 29 (87.9%) patients reported under this category, majority of the AEs were mild in severity in 25 (75.8%) patients.<br>Across studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, of the total 5499 AEs in 286 (84.1%) patients, majority of the AEs (5178) reported under this category were mild in severity in 216 (63.5%) patients. |
| Risk factors and risk groups: | Potential risk factors for injection site reactions: sites where pressure or rubbing may occur from clothing. This medicinal product should not be injected into tattoos, moles, birthmarks, bruises, rashes, or areas where the skin is tender, red, hard, bruised, damaged, burned, or inflamed. |
| Preventability: | Patients should be advised as to the possibility of injection site reactions and counselled on symptomatic interventions such as icing of the injection site prior to and after drug administration. |
| Impact on the risk-benefit balance of the product: | Although adverse events at the injection site are predominantly self-limiting, they may lead to non-adherence to the treatment regimen or discontinuation of treatment. |
| Public health impact: | The potential impact on the risk-benefit profile of volanesorsen is low because the injection site reactions are predominantly self-limiting. |

Abbreviations: AE = adverse event; FCS = familial chylomicronemia syndrome; HLT = High level term; LCRIS = local cutaneous reaction at injection site; MedDRA = Medical Dictionary for Regulatory Activities; SMQ = Standardised MedDRA Query

| **Important Potential Risk – Immunogenicity** | |
|---|---|
| Potential mechanisms: | In non FCS patients, Type 1 immediate hypersensitivity in the anaphylactic reaction report (IgE negative) and Type III delayed hypersensitivity reaction in the serum sickness/serum sickness-like reports are potential mechanisms. |

| **Important Potential Risk – Immunogenicity** | |
|---|---|
| Evidence source(s) and strength of evidence: | Studies CS2, CS4, CS6, CS7, CS16, CS17<br>CS6 and CS16 are the randomised controlled trials |
| Characterisation of the risk: | MedDRA search criteria: PTs: Drug specific antibody, Drug specific antibody present;<br>SMQ: Hypersensitivity (narrow)<br>Frequency<br>Of the 33 volanesorsen-treated patients in Study CS6, 10 (30%) patients tested positive for anti-drug antibodies (ADA) at some point during the study. There were 76 events reported in 7 (21.2%) patients in the volanesorsen group and 2 events were reported in 2 (6.1%) patients in placebo group.<br>Across studies CS2, CS6, CS16 and CS7, a total of 23 (25%) patients had 138 events in the category of immunogenicity. The most commonly reported events in this category were rash in 8 (8.7%) patients, injection site urticaria, urticaria, eczema each in 3 (3.3%) patients, injection site rash and hypersensitivity each in 2 (2.2%) patients.<br>In CS17 (non-FCS patients), a total of 14 AEs were reported in 6 (18.2%) patients. Eleven (11) of these AEs reported under this category were related to volanesorsen in 4 (12.1%) patients.<br>Across studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, a total of 59 (17.4%) patients had 211 events in the category of immunogenicity. One hundred and eighty eight (188) events were reported as related to volanesorsen in 43 (12.6%) patients.<br>Seriousness/outcomes<br>Two SAE reports of serum sickness-like reaction and serum sickness were reported in patients in CS2 and CS16, respectively; in addition, 1 patient in Study CS17 experienced an SAE of anaphylactic reaction. None of these patients had FCS. In 2 of the 3 cases (serum sickness and anaphylactic reaction), the patients tested positive for ADA prior to onset of the event. In all cases, the SAEs resolved upon discontinuation of volanesorsen.<br>Severity and nature of risk<br>In Study CS6, the median time of onset of immunogenicity in the 10 patients who became ADA-positive was 180 days and the median of individual patients' peak antibody titer was 400. The immunogenicity response was generally sustained from onset through the last evaluation except the placebo patient with pre-existing antibodies and 1 patient in the volanesorsen group. The demographics of patients who tested positive for ADA were similar to those who were negative, suggesting that immunogenicity incidence was not associated with a particular demographic characteristic. For patients who were ADA-positive during the study, there were no observed differences in TG reductions or common AEs.<br>In Study CS7, 51 subjects were in the treatment naïve group, and 17 subjects were in the volanesorsen combined group (consists of 14 subjects from CS6 and 3 subjects from CS16). For the treatment naïve group, 17 subjects were ADA positive, and 34 subjects were ADA negative. In seventeen ADA positive subjects, the median time to onset of ADA from the first treatment with volanesorsen was 302 days (range 85 to 815 days), and the median peak titer was 100 (range 50 to 6400). Five (36%) of the 14 CS6-volanesorsen subjects also tested positive for ADA, with a median time to onset from the first treatment with volanesorsen of 179 days (range 97 to 629 days) and median peak titer of 1600 (range 100 to 3200). None of the 3 CS16-volanesorsen subjects were ADA positive. The comparison of |

| **Important Potential Risk – Immunogenicity** | |
|---|---|
| | AE data, and laboratory data by ADA status was focused on the treatment naive group, as the sample size for the previously treated volanesorsen combined group (CS6 [14 subjects] and CS16 [3 subjects]) was low. Anti-drug antibodies were formed in 17 (33%) of 51 treatment naive subjects, but ADA was not associated with loss of efficacy nor did it impact the safety profile of volanesorsen.<br>In FCS patients, in addition to the observation that immunogenicity status does not appear to influence the safety of volanesorsen, there have been no reports of events characteristic of deposition of immune complexes in small blood vessels (e.g., vasculitis, SLE), in glomeruli/kidney (glomerulonephritis), or joints (spondyloarthropathies).<br>In Study CS17 (non FCS patients), of the total 14 AEs in 6 (18.2%) patients, majority of the AEs (5) reported under this category were mild in severity in 5 (15.2%) patients.<br>Across studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, 2 SAEs of sickness-like reaction and serum sickness were moderate in severity and 1 SAE of anaphylactic reaction was severe. |
| Risk factors and risk groups: | There are currently no known specific risk factors for immunogenicity associated with volanesorsen. |
| Preventability: | Volanesorsen is contraindicated in patients with a history of hypersensitivity to volanesorsen. |
| Impact on the risk-benefit balance of the product: | Anaphylactic reactions and serum sickness can be life-threatening events. Other allergic manifestations involving the skin (erythema, urticaria, wheals, rash) can be mild to severe in intensity. Management of these reactions may require treatment with antihistamines and steroids and have been fully reversible. |
| Public health impact: | There are no potential public health safety concerns due to the ultra-rare prevalence of FCS and uncommon occurrence of these events in FCS patients. |

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; FCS = familial chylomicronemia syndrome; IgE = immunoglobulin E; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SAE = serious adverse event; SLE = systemic lupus erythematosus; SMQ = Standardised MedDRA Query; TG = triglyceride

| **Important Potential Risk – Hepatotoxicity** | |
|---|---|
| Potential mechanisms | The liver is the pharmacodynamic target organ for volanesorsen distribution in both mice and monkeys. Kupffer cell hypertrophy/hyperplasia observed in the liver is likely an adaptive response related to uptake and clearance of exogenous materials and is not considered toxicologically significant or adverse (Braendli-Baiocco et al. 2017). |
| Evidence source(s) and strength of evidence | Studies CS2, , CS6, CS7, and CS16<br>CS6 and CS16 are the randomised controlled trials. |
| Characterisation of the risk | MedDRA search criteria: SMQ: Drug-related hepatic disorders - comprehensive search (narrow)<br>Frequency<br>In pivotal study CS6, 4 events in the hepatoxicity category were reported in 3 (9.1%) patients in volanesorsen group and 2 events were reported in 2 (6.1%) patients in placebo group. The incidence of a confirmed elevation in ALT to > 3×ULN was observed in 1 (3%) patient in the volanesorsen group during the on-treatment period. Patient 1941-1194 in the volanesorsen group had a baseline ALT value of 29 U/L and an ALT of 166 U/L at Week 19. The ALT elevation was |

| **Important Potential Risk – Hepatotoxicity** | |
|---|---|
| | associated with an AE of increased transaminases, which was mild in severity and was considered related to study drug by the Investigator. 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 patient in the volanesorsen group had an AST value > 3 ×ULN or total bilirubin > 2 ×ULN.<br><br>In CS16, a confirmed elevation in ALT to > 5 × ULN was observed in 2 (3%) patients in the volanesorsen group during the on-treatment period. Similarly, confirmed elevation in AST to > 5 × ULN was observed in 2 (3%) patients in the volanesorsen group during the on-treatment period. No patient in the volanesorsen group had an alkaline phosphatase (ALP) value > 2 × ULN or total bilirubin > 2 × ULN.<br><br>The only hepatic TEAEs occurring in more than 1 patient were alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased, each patient experiencing 1 event of AST and 1 event of ALT elevation.<br><br>All other hepatic-related AEs were assessed as mild except for an event of international normalised ratio (INR) increased assessed as moderate. The AEs of INR increased and hepatic enzymes increased were assessed as related. No hepatic TEAEs were reported as serious.<br><br>In study CS7, based on central lab values, no patient in any treatment group had shifts in ALT from ≤ 5 × ULN to ≥ 5.1 × ULN, however shifts were noted in AST from ≤ 5 × ULN at baseline to 5.1 - 10 × ULN for 1 (2%) patient in the treatment naïve group. This patient had a single increase of AST (184 U/L, > 5 x ULN, reference 9-34 U/L) that was accompanied by an increase in ALT (141 U/L, > 3 x ULN, reference 6-41 U/L), without an increase in serum bilirubin (0.4 mg/dL [reference range 6-44 mg/dL]) at Week 58, however the patient did not discontinue the study treatment, as the treatment discontinuation recommendation per SmPC labeling of a single increase in ALT or AST > 5 x ULN, which persists for ≥ 2 weeks, or lesser increases in ALT or AST that are associated with total bilirubin of > 2 x ULN were not met.<br><br>Across studies CS2, CS6, CS16 and CS7, a total of 12 (13%) patients had 20 events in the category of hepatotoxicity. The most commonly reported event under this category was alanine aminotransferase increased in 6 (6.5%) patients, aspartate aminotransferase increased in 5 (5.4%) patients, and transaminases increased in 3 (3.3%) patients. In CS17 study (non FCS patients), a total of 4 events under the category of hepatotoxicity were reported in 3 (9.1%) patients. Two (2) of these AEs were related to volanesorsen.<br><br>Across studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, a total of 29 (8.5%) patients had 41 events in the category of hepatotoxicity. Thirteen (13) events were related to volanesorsen in 12 (3.5%) patients.<br><br><u>Seriousness/outcomes</u><br><br>Across studies CS2, CS6, CS16 and CS7, no patient experienced events in this category that were related to treatment with volanesorsen. One (1.1%) patient has experienced serious event of drug-induced liver injury which was unrelated to treatment with volanesorsen and was resolved. A total of 17 AEs were resolved in 9 (9.8%) patients.<br><br>In CS17 study (non FCS patients), no patients reported any serious SAEs under this category. All the AEs reported under this category were resolved and none led to discontinuation of volanesorsen. |

| **Important Potential Risk – Hepatotoxicity** | |
|---|---|
| | Across studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, 2 AEs resulted in treatment discontinuation in 2 (0.6%) patients.<br>Severity and nature of risk<br>No events related to increased ALT, AST, or bilirubin increases led to discontinuation of treatment. There was no increased incidence of transaminase elevations above 3 × ULN in anti-volanesorsen antibody-positive patients. There was no pattern of observed trends in liver test results post volanesorsen dose (e.g., time to onset). There were no cases of transaminase elevations concurrently observed with rash, or eosinophilia.<br>Drug-induced liver injury (FDA 2009) based on Hy's Law has not been observed among FCS patients treated with volanesorsen. One patient in Study CS6 experienced drug-induced liver injury that was assessed to be caused by concomitant diclofenac.<br>Across studies CS2, CS6, CS16 and CS7, all TEAEs under the category of hepatotoxicity were mild to moderate in severity and only 2 TEAEs hepatic enzyme increased and liver injury resulted in discontinuation in 2 (0.6%) patients.<br>In CS17 study (non FCS patients), all the AEs reported under this category were mild in severity.<br>Across studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, of the total 41 AEs reported under this category in 29 (8.5%) patients, the majority of the AEs (30) in 22 (6.5%) patients were mild in severity. |
| Risk factors and risk groups | There are no known specific risk factors for elevated transaminases observed during treatment with volanesorsen. Alcohol ingestion, concomitant medications and fatty liver disease may be contributing factors. |
| Preventability | Monitoring for evidence of hepatotoxicity by assessment of liver function tests (serum) should be performed on a quarterly basis.<br>Avoidance of alcohol and hepatotoxic medications. |
| Impact on the risk-benefit balance of the product | Liver injury may be mild to severe in nature and could result in hospitalisation and also could be life threatening. The hepatic AEs experienced have been reversible. |
| Public health impact | There are no potential public health safety concerns due to the ultra-rare prevalence of FCS and uncommon occurrence of these events in FCS patients. |

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; FCS = familial chylomicronemia syndrome; INR = international normalised ratio; MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; SLE = systemic lupus erythematosus; SMQ = Standardised MedDRA Query; TEAE = treatment emergent adverse events; TG = triglyceride; ULN = upper limit of normal

| **Important Potential Risk – Nephrotoxicity** | |
|---|---|
| Potential mechanisms: | Volanesorsen is concentrated within the kidney. |
| Evidence source(s) and strength of evidence: | Studies CS2, CS6, CS7, and CS16<br>CS6 and CS16 are the randomised controlled trials |
| Characterisation of the risk: | MedDRA search criteria: SMQs: Acute renal failure (broad and narrow), Chronic kidney disease (broad and narrow)<br>Frequency<br>In pivotal study CS6, 6 events in the nephrotoxicity category were reported in 4 (12.1%) patients in volanesorsen group and 1 event was reported in 1 (3.0%) patients in placebo group. None of the AEs under this category were serious. |

| **Important Potential Risk – Nephrotoxicity** | |
|---|---|
| | In the volanesorsen group (study CS6), 3 (9%) patients had a serum creatinine value increase ≥0.3 mg/dL from baseline and 1 (3%) patient had a ≥50% increase over the baseline value during the on-treatment period. For 2 of the 4 patients, these elevations were transient, occurring at a single time point. None of these elevations led to study treatment discontinuation. In comparison, none of the patients in the placebo group were reported to have serum creatinine values that met these criteria. None of the patients had serum creatinine ≥0.3 mg/dL or 50% or higher than baseline at the final visit.<br><br>Eight events of proteinuria, of varying severity, have been reported in 5 patients, in CS7: 4 (mild), 3 (moderate) and 1 (severe).One patient had 2 events (one mild and one moderate), another patient had 2 events (one moderate and one severe) and one other patient had 2 events, both mild in severity. The remaining 2 patients had one event each of proteinuria (one mild and one moderate). No action was taken with the study drug for the mild and moderate proteinuria events. All proteinuria events were assessed as not related with exception of the severe TEAE of proteinuriawhich was assessed as possibly related. The patient with severe TEAE of proteinuria experienced mild proteinuria 20 days prior to starting the study drug. 11 days after initiating the study drug, the subject experienced severe or worsening proteinuria. The study drug was permanently discontinued due to severe proteinuria. Approximately one year later, the severe non-serious TEAE of worsening proteinuria was considered serious as the subject was hospitalized for seven days for renal biopsy and further investigation into worsening proteinuria. The subject reportedly had markedly elevated proteinuria of 3.24 g/24 hours (local laboratory, reference range 0.00-0.15 g/24 hours). Approximately 8 months from the last dose of the study drug, the subject was diagnosed with “Multifocal segmental glomerulonephritis,” which was confirmed with a renal biopsy. The renal biopsy revealed a diagnosis of focal segmental glomerular sclerosis likely due to ischaemic pathogenesis (alternative aetiology from volanesorsen). Following this diagnosis, the investigator amended the reported term proteinuria/worsening proteinuria to ‘Multifocal segmental glomerulosclerosis’ and changed the causality of the SAE from possibly related to remote/unlikely related to study drug. No other patients were discontinued from study treatment due to renal-related AEs. One subject reported Urine Protein/Creatinine ratio (UPCR) increased, which was mild in severity, and no action was taken with the study drug.<br><br>Two subjects reported 3 events of albuminuria. All 3 albuminuria events were mild in severity. No action was taken with the study drug. Of the 3 albuminuria events, 2 events were recovered, and 1 event was not recovered.<br><br>There has been minimal impact on the laboratory shift tables (Urine albumin and protein) due to the adverse events of Proteinuria and Albuminuria.<br><br>Across Studies CS2, CS6, CS16 and CS7, a total of 15 (16.3%) patients had 24 events in the category of nephrotoxicity. The most commonly reported event under this category was proteinuria in 5 (5.4%) patients, albuminuria, creatinine renal clearance decreased, urine output decreased each in 2 (2.2%) patients.<br><br>At any time during the study CS7, serum creatinine values were ≥ 0.3 mg/dL higher than baseline for 7 (10%) patients overall, including 4 (8%) treatment-naïve, 2 (14%) CS6-volanesoren patients, and 1 (33%) CS16-patient; and ≥ 50% higher than Baseline for 3 (4%) patients overall, including 1 (2%) treatment-naïve and 2 (14%) CS6-volanesorsen patients. No patient had serum creatinine values ≥ 0.3 mg/dL or ≥ 50% higher than baseline at the final visit. There were no reported TEAEs related to creatinine values. |

| **Important Potential Risk – Nephrotoxicity** | |
|---|---|
| | In Study CS17 (non FCS patients), a total of 17 AEs in this category were reported in 8 (24.2%) patients. One SAE of blood creatinine increased was related to the use of volanesorsen.<br>Across Studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, a total of 35 (10.3%) patients had 55 events under the category of nephrotoxicity. Of these 9 events in 5 (1.5%) patients were related to volanesorsen.<br>Seriousness/outcomes<br>Across Studies CS2, CS6, CS16 and CS7, a SAE of worsening proteinuria was reported in a patient in CS7 who previously received volanesorsen treatment in CS6. This patient was discontinued from volanesorsen treatment in CS7 due to severe proteinuria and renal biopsy revealed a diagnosis of multifocal segmental glomerularsclerosis) likely due to ischaemic pathogenesis (alternative aetiology from volanesorsen). The SAE of focal segmental glomerulosclerosis was ongoing. As of 17 Nov 2021, the events in the category of nephrotoxicity were ongoing in 8 (8.7%) patients and resolved in 7 (7.6%) patients.<br>In Study CS17 (non FCS patients), the SAE of blood creatinine increased was resolved and did not lead to discontinuation of volanesorsen.<br>Across Studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, no additional SAEs were reported.<br>Severity and nature of risk<br>Across Studies CS2, CS6, CS16 and CS7, all AEs reported within this category were mild or moderate in severity with the exception of the worsening of proteinuria which was severe.<br>In Study CS17 (non FCS patients), of the total 17 AEs, the majority of the AEs (16) reported under this category were mild in severity in 7 (21.2%) patients and only one SAE of blood creatinine increased was severe. |
| Risk factors and risk groups: | There are no known specific risk factors for abnormal renal function tests observed during treatment with volanesorsen.<br>Dehydration, diabetes mellitus and concomitant nephrotoxic medications may be contributing factors. |
| Preventability: | Monitoring for evidence of nephrotoxicity by routine urine dipstick will take place on a quarterly basis. In the case of a positive assessment, a broader assessment of renal function, including a 24hr-collection to quantify the proteinuria and assess creatinine clearance will also be required.<br>Maintenance of hydration and avoidance of concomitant use of nephrotoxic agents. |
| Impact on the risk-benefit balance of the product: | Renal AEs could result in hospitalisation and also could be life-threatening. The renal AEs experienced have been reversible. |
| Public health impact: | There are no potential public health safety concerns due to the ultra-rare prevalence of FCS and uncommon occurrence of these events in FCS patients. |

Abbreviations: AE = adverse event; eGFR = estimated Glomerular Filtration rate; FCS = familial chylomicronemia syndrome; MedDRA = Medical Dictionary for Regulatory Activities; Na = sodium; K = potassium; SAE = serious adverse event; SMQ = Standardised MedDRA Query; TEAE = treatment emergent adverse event

## SVII.3.2. Presentation of the Missing Information

| **Missing Information – Use in Pregnancy and Lactation** | |
|---|---|
| Evidence source | There are no clinical data available for use of volanesorsen in women who are pregnant or nursing. |
| Population in need of further characterisation | Pregnant or nursing mothers with FCS. |

Abbreviation: FCS = familial chylomicronemia syndrome

| **Missing Information – Use in Patients with Hepatic Impairment** | |
|---|---|
| Evidence source | There are no clinical data available for use of volanesorsen in patients with hepatic impairment. |
| Population in need of further characterisation | FCS patients with hepatic impairment. |

Abbreviation: FCS = familial chylomicronemia syndrome

| **Missing Information – Use in Patients with Severe Renal Impairment** | |
|---|---|
| Evidence source | There are no clinical data available for use of volanesorsen in patients with severe renal impairment. A population PK analysis suggests that mild and moderate renal impairment has no clinically relevant effect on the systemic exposure of volanesorsen. |
| Population in need of further characterisation | FCS patients with severe renal impairment. |

Abbreviations: FCS = familial chylomicronemia syndrome; PK = pharmacokinetic

| **Missing Information – Long Term Safety** | |
|---|---|
| Evidence source | Across Studies CS2, CS6, CS16, and CS7, 50 patients have been treated with volanesorsen for >1 year. At this time it is unknown whether prolonged exposure to volanesorsen will alter the benefit-risk profile of the drug. |
| Population in need of further characterisation | Patients receiving volanesorsen for more than 1 year. |

| **Missing Information – Use in the Elderly** | |
|---|---|
| Evidence source | Across Studies CS2, CS6, CS16 and CS7 (in FCS patients), of the 92 patients enrolled and treated in these studies, 8 (8.7%) were aged 65 or over, while 84 (91.3%) were younger than 65 years. Of the 340 patients enrolled and treated in Studies CS1, CS13, CS2, CS4, CS16, CS6, CS7 and CS17, 28 (8.2%) patients aged ≥ 65 years were treated with volanesorsen. It was noted that patients ≥ 65 years experienced fewer AEs than younger patients.<br>In study CS7, 62 subjects were under 65 years of age, while 6 subjects were aged 65 or older. The younger age group (< 65 years of age) reported a greater proportion of AEs (62 subjects reported 2677 AEs) than the older age group of > 65 years of age (6 subjects reported 162 AEs). The proportion of bleeding events for the younger age group (31 subjects [50.0%]) was the same as the older age group (3 subjects [50.0%]). |

| **Missing Information – Use in the Elderly** | |
|---|---|
| | The overall conclusion is that no differences in safety, PK, or effectiveness were observed between elderly patients and younger patients. |
| Population in need of further characterisation | Elderly patients aged 65 years or more with FCS. |

Abbreviations: AE = adverse event; FCS=familial chylomicronemia syndrome; PK=pharmacokinetic

# PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

A summary of the safety concerns identified during the clinical programme is provided in the table below.

| **Summary of Safety Concerns** | |
|---|---|
| Important identified risks | Thrombocytopenia<br>Injection site reactions |
| Important potential risks | Immunogenicity<br>Hepatotoxicity<br>Nephrotoxicity |
| Missing information | Use in pregnancy and lactation<br>Use in patients with hepatic impairment<br>Use in patients with severe renal impairment<br>Long-term safety<br>Use in elderly |

# PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTORISATION SAFETY STUDIES)

## III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:

**Specific adverse reaction follow-up questionnaires for thrombocytopenia, injection site reactions, hepatotoxicity (hepatic adverse events questionnaire), immunogenicity (hypersensitivity questionnaire), and renal toxicity (renal adverse events questionnaire). Follow up questionnaire for non-important risk for constitutional symptoms is also included:**

Structured follow-up questionnaire forms are used to obtain further information regarding reported suspected adverse reactions of thrombocytopenia, injection site reactions, immunogenicity, hepatotoxicity, nephrotoxicity, and constitutional symptoms. The forms have been designed to collect information pertaining to the clinical course of the event, the signs and symptoms observed, volanesorsen treatment received, relevant medical and social history, concomitant medications, risk factors and relevant baseline, interim and event-related laboratory results. The follow-up questionnaire forms are provided in see Annex 4 of this EU RMP.

**Other forms of routine pharmacovigilance activities for thrombocytopenia:**

The frequency of monitoring aggregate data will be via a monthly safety review, but if the number of cases was deemed high, an earlier meeting would occur.

The following thrombocytopenia-related events will be expedited adverse events of special interest and individual case safety reports will be expedited to the regulatory authorities within 15 calendar days:

- Severe thrombocytopenia (platelet count of $<50\times10^9$/L)
- Serious bleeding events associated with death, life-threatening nature, or hospitalisation

## III.2 Additional Pharmacovigilance Activities

### WAY4001: WAYLIVRA® Post-Authorisation Safety Study (PASS) and Product Registry

The WAYLIVRA® Post-Authorisation Safety Study (PASS) and Product Registry will enrol patients treated with WAYLIVRA. The registry protocol synopsis is provided in Annex 3.

This registry will enrol patients treated with WAYLIVRA and will monitor the incidence and risk of thrombocytopenia (and any bleeding outcomes associated with thrombocytopenia), as well as adherence with platelet monitoring and dose adjustment requirements in the SmPC. The registry will also monitor hepatotoxicity, renal toxicity, immunogenicity, inflammatory/immunologic events, injection site reactions, safety in elderly patients, in patients with renal or hepatic impairment, outcomes in WAYLIVRA-exposed pregnancies, and the long term safety profile of WAYLIVRA. Efficacy outcomes in terms of triglyceride reduction and clinical outcomes of pancreatitis events, reduction in abdominal pain frequency and severity will also be monitored along with the effect of WAYLIVRA on health related quality of life.

**Study WAY4001**

Study short name and title:

WAY4001: WAYLIVRA® Post-Authorisation Safety Study (PASS) and Product Registry

**Rationale and study objectives:**

The aim of this study (PASS phase and WAYLIVRA product registry phase) is to further characterise the safety and effectiveness of WAYLIVRA in patients with FCS under real-world conditions.

Primary objective:

- To evaluate the safety of WAYLIVRA on severe thrombocytopenia and bleeding in FCS patients according to the dose recommendation and dose algorithm in the SmPC

Secondary objectives:

- To determine real-world incidence rates of mild, moderate and severe thrombocytopenia and associated bleeding events, overall and by event grading
- To describe prescribers' adherence to recommendations for platelet monitoring and dose reduction to minimise the risk of thrombocytopenia as outlined in the SmPC
- To determine real-world incidence rates and severity of:
    - immunogenicity/immunological events
    - hepatotoxicity
    - renal toxicity
    - severe injection site reactions
    - mild, moderate and severe thrombocytopenia with or without an associated serious bleeding episode in patients weighing less than 70kg, overall and by event grading
- To describe the safety profile in the following patient sub-groups for patients treated with WAYLIVRA:
    - patients with hepatic impairment
    - patients with renal impairment
    - elderly patients (≥ 65 years of age)
- To describe the long-term safety profile of WAYLIVRA
- To describe outcomes for WAYLIVRA-exposed pregnancies; specifically, gestational outcomes (e.g., live birth, spontaneous abortion, etc.) and major congenital malformations observed at pregnancy conclusion

Secondary Efficacy Objectives

- To evaluate the long-term efficacy of WAYLIVRA with respect to triglyceride reduction, pancreatitis prevention, and reduction in abdominal pain frequency and severity

- To evaluate the effect of WAYLIVRA on health-related quality of life assessed by FCS-related symptoms and impacts on daily lives

**Study design:**

This study will be conducted in two phases. The first phase of the study is the PASS phase and will be concluded after a study term of 7 years or earlier if data collected amounts to 247 person-years of exposure in patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate have been collected.

Following the PASS phase, the study will continue as the WAYLIVRA Product Registry, or the Registry phase, which will be conducted throughout the commercial life of the drug, to obtain long-term data on safety and efficacy of WAYLIVRA.

In both phases of the study, real-world data will be collected on FCS patients prescribed WAYLIVRA.

This study is designed as a non-interventional observational study. All patients will receive care according to normal clinical practice and clinical care will not be mandated by the protocol. As such, the decision to prescribe WAYLIVRA is separate from the decision to include the patient in the study and patients are not required to undergo any additional diagnostic or monitoring procedures.

**Study population:**

Patients in Europe with FCS who have initiated or who are initiating treatment with commercial WAYLIVRA, will be recruited to participate in this study. Clinical sites will be asked to invite all patients who meet study eligibility criteria to enrol.

**Inclusion Criteria:**

Eligible patients must meet the following criteria:

- Adult patients (≥ 18-years-old) prescribed WAYLIVRA
- Have provided written informed consent

**Exclusion Criteria:**

None

**Germany-Specific Eligibility Criteria:**

The following eligibility criteria are specific to patients who reside in Germany and who consent to participate this study.

Inclusion Criteria
1. Adult patients (≥ 18-years-old) prescribed WAYLIVRA ®in accordance with the approved Summary of Product Characteristics.
2. Treated in Germany.
3. Have provided written informed consent.

Exclusion Criteria

- Patients for whom WAYLIVRA is not advised including:
- Patients with chronic or unexplained thrombocytopenia. Treatment should not be initiated in patients with thrombocytopenia (platelet count < 140 × $10^9$/L).
- Patients with hypersensitivity to the active substance or to any of the following excipients:
    - Sodium hydroxide (for pH adjustment).
    - Hydrochloric acid (for pH adjustment).

## Milestones

| Milestone | Planned/Completed Date | Comments |
|---|---|---|
| Protocol Submission | 03 June 2019 | - |
| Final Protocol After Pharmacovigilance Risk Assessment Committee (PRAC) Review | 31 July 2020 | - |
| Registration in EU PAS Register | 01 September 2020 | - |
| Start of PASS Phase Data Collection | 04 December 2020 | - |
| Interim Reports of the PASS | Annually | Annual interim reports will be submitted in alignment with the annual conditional market authorization renewal. |
| End of Data Collection for PASS Phase and Start of Registry Phase Data Collection | Q4 2027 | 7 years from start of data collection or earlier if data collected amounts to 247 person-years. |
| PASS Phase Study Report | Q4 2028 | One year from end of PASS Phase |
| Interim Reports of the Registry | Where applicable | To be included in the Periodic benefit-risk evaluation reports (PBRERs) |
| End of Data Collection for Registry Phase | Not applicable | End of commercial life of the medicinal product |
| Registry Phase Study Report | Not applicable | One year from End of Registry Phase |

Abbreviations: EU PAS Register = European Union electronic Register of Post-Authorisation Studies; PASS = post-authorisation safety study; PBRER = periodic benefit-risk evaluation reports; PRAC = Pharmacovigilance Risk Assessment Committee

# III.3 Summary Table of Additional Pharmacovigilance Activities

## Table 35: Ongoing and Planned Additional Pharmacovigilance Activities

| Study / Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Category 2** - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances authorisation | | | | |
| WAY4001 - WAYLIVRA® Post-Authorisation Safety Study (PASS) and Product Registry / Planned | Primary objective:<br>• To evaluate the safety of WAYLIVRA on thrombocytopenia and bleeding in FCS patients according to the dose recommendation and dose algorithm in the Summary of Product Characteristics<br><br>Secondary objectives:<br>• To determine real-world incidence rates of mild, moderate and severe thrombocytopenia, and associated bleeding events, overall and by event grading<br>• To describe prescribers' adherence to recommendations for platelet monitoring and dose adjustment requirements per the WAYLIVRA SmPC<br>• To determine real-world incidence rates and severity of immunogenicity/immunological events, hepatotoxicity, renal toxicity, severe injection site reactions, and mild, moderate and severe thrombocytopenia with or without an associated serious bleeding episode in patients weighing less than 70kg, overall and by event grading<br>• To describe the safety profile of WAYLIVRA in patients with renal | • Thrombocytopenia<br>• Injection site reactions<br>• Immunogenicity<br>• Hepatotoxicity<br>• Nephrotoxicity<br>• Use in patients with hepatic impairment<br>• Use in patients with severe renal impairment<br>• Use in elderly<br>• Long-term safety<br>• Use in pregnancy and lactation | 1. Protocol Submission<br>2. Final Protocol After PRAC Review<br>3. Registration in EU PAS Register<br>4. Start of PASS Phase Data Collection<br>5. Interim Reports of the PASS<br>6. End of Data Collection for PASS Phase and Start of Registry Phase Data Collection<br>7. PASS Phase Study Report<br>8. Interim Reports of the Registry<br>9. End of Data Collection for Registry Phase<br>10. Registry Phase Study Report | 1. 03 June 2019<br>2. 31 July2020<br>3. 01 September 2020<br>4. 04 December 2020<br>5. Annually<br>6. Q4 2027<br>7. Q4 2028<br>8. Where applicable (To be included in the Periodic benefit risk evaluation reports [PBRERs])<br>9. Not applicable (End of commercial life of the medicinal product)<br>10. Not applicable (One year from End of Registry Phase) |

| Study / Status | Summary of Objectives | Safety Concerns Addressed | Milestones | Due dates |
|---|---|---|---|---|
| | impairment, hepatic impairment, and elderly patients (ages ≥65 years) who receive WAYLIVRA<br>• To describe the long-term safety profile of WAYLIVRA<br>• To describe outcomes for WAYLIVRA-exposed pregnancies; specifically, gestational outcomes (e.g., live birth, spontaneous abortion, etc.) and major congenital malformations observed at pregnancy conclusion<br>Secondary Efficacy Objectives<br>• To evaluate the long-term efficacy of WAYLIVRA with respect to triglyceride reduction, pancreatitis prevention, and reduction in abdominal pain frequency and severity<br>• To evaluate the effect of WAYLIVRA on health-related quality of life assessed by FCS-related symptoms and impacts on daily lives | | | |

Abbreviations: EU PAS Register = European Union electronic Register of Post-Authorisation Studies; FCS = familial chylomicronemia syndrome; PASS = post-authorisation Safety Study; PBRER = periodic benefit-risk evaluation reports; PRAC = Pharmacovigilance Risk Assessment Committee; SmPC = Summary of Product Characteristics

# PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

## IV. 1 Applicability of Efficacy to All Patients in the Target Population

Not applicable.

## IV. 2 Tables of Post-authorisation Efficacy Studies

Not applicable.

## IV. 3 Summary of Post-authorisation Efficacy Development Plan

Not applicable.

## IV. 4 Summary of Completed Post-authorisation Efficacy Studies

Not applicable.

# PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE RISK MINIMISATION ACTIVITIES)

## V. 1 Routine Risk Minimisation Measures

| **Safety concern** | **Routine risk minimisation activities** |
|---|---|
| Thrombocytopenia | Routine risk communication:<br>• SmPC section 4.4, 4.8<br>• PL section 4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Recommendations for platelet count monitoring in SmPC sections 4.2, and 4.4 and notification of platelet count monitoring to patients in PL section 2.<br>• Treatment recommendations with volanesorsen in case of low platelet counts in SmPC section 4.2.<br>• Contraindication for initiating the treatment with volanesorsen in patients with thrombocytopenia (platelet count < 140 x $10^9$/L) in SmPC section 4.3 and PL section 2.<br>• Caution advised for the use of volanesorsen in patients deemed at higher risk of thrombocytopenia in SmPC section 4.4 and 4.5.<br>• Recommendation to discontinue antiplatelet medicinal products/NSAIDs/anticoagulants for platelet levels <75 x $10^9$/L and instruction to discontinue at <50 x $10^9$/L in SmPC section 4.4 and 4.5.<br>• Instructions for patients to notify their doctor if they are taking any medications that can lower platelet count or stop the blood from clotting in PL section 2.<br>• Instructions for patients to monitor for and notify their doctors immediately if they experience any signs or symptoms of thrombocytopenia or a serious bleed in SmPC section 4.4 and PL sections 2 and 4.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: Prescription only medicine. |
| Injection site reactions | Routine risk communication:<br>• SmPC section 4.2 and 4.8<br>• PL section 4<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Instructions on the method of administration in Section 4.2 of SmPC.<br>Other routine risk minimisation measures beyond the Product Information: |

| | |
|---|---|
| | • Legal status: Prescription only medicine. |
| Immunogenicity | Routine risk communication:<br>• SmPC section 4.4.<br>• PL section 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Recommendation to contact Marketing Authorisation Holder to discuss antibody testing, if formation of anti-drug antibodies with a clinically significant effect is suspected in section 4.4 of SmPC.<br>• Recommendation to monitor inflammation through quarterly assessment of erythrocyte sedimentation rate in section 4.4 of SmPC.<br>• Contraindication for initiating the treatment with volanesorsen if the patient is hypersensitive to the active substance or to any of the excipients in section 4.3 of SmPC and PL section 2.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: Prescription only medicine. |
| Hepatotoxicity | Routine risk communication:<br>• SmPC section 4.4.<br>• PL sections 2 and 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Recommendation for monitoring hepatotoxicity is included in SmPC section 4.4 and PL section 2.<br>• Caution advised for the use of volanesorsen in patients with any liver problems in PL section 2.<br>• How to detect signs and symptoms of liver damage in PL sections 2 .<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: Prescription only medicine. |
| Nephrotoxicity | Routine risk communication:<br>• SmPC section 4.4.<br>• PL sections 2 and 4.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Recommendation for monitoring for nephrotoxicity is included in SmPC section 4.4.<br>• Caution advised for the use of volanesorsen in patients with any kidney problems in PL section 2.<br>• How to detect signs and symptoms of kidney damage in PL section 2.<br>Other routine risk minimisation measures beyond the Product Information: |

| | |
|---|---|
| | • Legal status: Prescription only medicine. |
| Use in pregnancy and lactation | Routine risk communication:<br>• SmPC section 4.6.<br>• PL section 2.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Recommendations to avoid to avoid the use of volanesorsen during pregnancy in SmPC section 4.6 and PL section 2.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: Prescription only medicine. |
| Use in patients with hepatic impairment | Routine risk communication:<br>• SmPC section 4.2 and 5.2.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• None.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: Prescription only medicine. |
| Use in patients with severe renal impairment | Routine risk communication:<br>• SmPC sections 4.2 and 5.2.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• Recommendations for closely observing patients with renal impairment in SmPC section 4.2.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: Prescription only medicine. |
| Long-term safety | Routine risk communication:<br>• None.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• None.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: Prescription only medicine. |
| Use in elderly | Routine risk communication:<br>• SmPC sections 4.2, 5.1, and 5.2.<br>Routine risk minimisation activities recommending specific clinical measures to address the risk:<br>• None.<br>Other routine risk minimisation measures beyond the Product Information:<br>• Legal status: Prescription only medicine. |

Abbreviations: PL = package leaflet; SmPC= Summary of Product Characteristics

# V. 2 Additional Risk Minimisation Measures

### Healthcare Professional and Patient/Carer Guide

Objectives:

Provision of educational material to healthcare providers, patients and carers.

Rationale for the additional risk minimisation activity:

This information outlines the importance of platelet monitoring and dose frequency adjustment on signs and symptoms of bleeding, and on the need to seek immediate treatment.

List of addressed safety concerns:

- Thrombocytopenia

Target audience and planned distribution path:

Educational materials are available for potential prescribers, patients and carers and will include information on participation in the WAYLIVRA® PASS and Product Registry (WAY4001).

As per the revised distribution methodology for the additional risk minimisation measures (aRMMs), the finished product along with the educational package will be packed and shipped from local warehouses in Europe. The revised distribution methodology for the aRMMs will maintain control of the drug and associated educational materials in a safe, effective and compliant manner. The educational programme is:

- Comprehensive in content and includes product labeling and additional educational materials.
- Comprehensive across different types of data sources including spontaneous reports and organised data collection systems.
- Includes ongoing efforts to measure adherence with the treatment algorithm by HCPs.
- Designed to be efficient in communicating significant non-adherence incidents to the CHMP/PRAC on an ongoing basis via enhanced pharmacovigilance and periodic safety or study reports.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness of the educational programme will be measured by evaluating data (platelet test results, WAYLIVRA dosing information and platelet testing frequency).

- Evaluation of non-adherence rates with the treatment algorithm in organised data collection systems – WAYLIVRA® PASS and Product Registry (WAY4001).
- Monitoring non-adherence incidents spontaneous reporting rate trends

The primary criteria are:

- Rates of non-adherence with the treatment algorithm and association of non-adherence with any serious bleeding events.

Planned dates for assessment

WAY4001 interim reports will be submitted with the annual conditional market authorisation renewal. PASS phase final study report is planned by Q4 2028 (1 year from end of PASS phase). Interim Reports of the Registry are planned where applicable (to be included in PBRERs). End of Data Collection for Registry Phase will be End of commercial life of the medicinal product. A Registry Phase Study Report will be one year from End of Registry Phase.

## V. 3 Summary Table of Risk Minimisation Measures

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important identified risks** | | |
| Thrombocytopenia | Routine risk minimisation measures:<br>• SmPC section 4.4 4.8<br>• PL section 4<br>• Recommendations for platelet count monitoring in SmPC sections 4.2, and 4.4 and notification of platelet count monitoring to patients in PL section 2.<br>• Treatment recommendations with volanesorsen in case of low platelet counts in SmPC section 4.2.<br>• Contraindication for initiating the treatment with volanesorsen in patients with thrombocytopenia (platelet count < 140 x $10^9$/L) in SmPC section 4.3 and PL section 2.<br>• Caution advised for the use of volanesorsen in patients deemed at higher risk of thrombocytopenia in SmPC section 4.4 and 4.5.<br>• Recommendation to discontinue antiplatlet medicinal products/NSAIDs/anticoagulants for platelet levels <75 x $10^9$/L and instruction to discontinue at <50 x $10^9$/L in SmPC section 4.4 and 4.5 | Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:<br>• Adverse reaction follow-up questionnaire form.<br>• Expedited safety reporting (within 15 calendar days) to Regulatory Authorities of ICSRs that meet the following criteria:<br>○ Severe thrombocytopenia (<50×$10^9$/L)<br>○ Serious bleeding events associated with death, life-threatening nature, or hospitalisation.<br>Additional pharmacovigilance activities:<br>• WAY4001 - WAYLIVRA® PASS and Product Registry (final PASS study report is expected by Q4 2028(1 year from end of PASS phase). |

| | | |
|---|---|---|
| | • Instructions for patients to notify their doctor if they are taking any medications that can lower platelet count or stop the blood from clotting in PL section 2.<br>• Instructions for patients to monitor for and notify their doctors immediately if they experience any signs or symptoms of thrombocytopenia or a serious bleed in SmPC section 4.4 and PL sections 2 and 4.<br>• Legal status: Prescription only medicine.<br>Additional risk minimisation measures:<br>• HCP guide and Patient/Carer Guide | |
| Injection site reactions | Routine risk minimisation measures:<br>• SmPC section 4.2 and 4.8.<br>• PL section 4.<br>• Instructions on the method of administration in section 4.2 of SmPC.<br>• Legal status: Prescription only medicine.<br>Additional risk minimisation measures:<br>• None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>• Adverse reaction follow-up questionnaire form.<br>Additional pharmacovigilance activities:<br>• WAY4001 - WAYLIVRA® PASS and Product Registry (final PASS study report is expected by Q4 2028(1 year from end of PASS phase). |

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Important potential risks** | | |
| Immunogenicity | Routine risk minimisation measures:<br>• SmPC section 4.4.<br>• PL section 4.<br>• Recommendation to contact Marketing Authorisation Holder to discuss antibody testing, if formation of anti-drug antibodies with a clinically significant effect is suspected in section 4.4 of SmPC.<br>• Recommendation to monitor inflammation through quarterly assessment of erythrocyte sedimentation rate in section 4.4 of SmPC.<br>• Contraindication for initiating the treatment with volanesorsen if the patient is hypersensitive to the active substance or to any of the excipients in section 4.3 of SmPC and PL section 2.<br>• Legal status Prescription only medicine.<br>Additional risk minimisation measures:<br>• None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>• Adverse reaction follow-up questionnaire form.<br>Additional pharmacovigilance activities:<br>• WAY4001 - WAYLIVRA® PASS and Product Registry (final PASS study report is expected by Q4 2028(1 year from end of PASS phase). |
| Hepatotoxicity | Routine risk minimisation measures:<br>• SmPC section 4.4.<br>• PL sections 2 and 4.<br>• Recommendation for monitoring hepatotoxicity is included in SmPC section 4.4 and PL section 2.<br>• Caution advised for the use of volanesorsen in patients with any liver problems in PL section 2.<br>• How to detect signs and symptoms of liver damage in PL sections 2.<br>• Legal status Prescription only medicine.<br>Additional risk minimisation measures:<br>• None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>• Adverse reaction follow-up questionnaire form<br>Additional pharmacovigilance activities:<br>• WAY4001 - WAYLIVRA® PASS and Product Registry (final PASS study report is expected in Q4 2028(1 year from end of PASS phase). |

| | | |
|---|---|---|
| Nephrotoxicity | Routine risk minimisation measures:<br>• SmPC section 4.4.<br>• PL sections 2 and 4.<br>• Recommendation for monitoring for nephrotoxicity is included in SmPC section 4.4.<br>• Caution advised for the use of volanesorsen in patients with any kidney problems in PL section 2.<br>• How to detect signs and symptoms of kidney damage in PL section 2.<br>• Legal status: Prescription only medicine.<br>Additional risk minimisation measures:<br>• None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>• Adverse reaction follow-up questionnaire form.<br>Additional pharmacovigilance activities:<br>• WAY4001 - WAYLIVRA® PASS and Product Registry (final PASS study report is expected by Q4 2028(1 year from end of PASS phase). |

Abbreviations: PASS = post-Authorisation Safety Study; NSAIDs= nonsteroidal anti-inflammatory drugs; PL=Package leaflet; SmPC= Summary of Product Characteristics

| Safety Concern | Risk Minimisation Measures | Pharmacovigilance Activities |
|---|---|---|
| **Missing information** | | |
| Use in pregnancy and lactation | Routine risk minimisation measures:<br>• SmPC section 4.6.<br>• PL section 2.<br>• Recommendations to avoid to avoid the use of volanesorsen during pregnancy in SmPC section 4.6 and PL section 2.<br>• Legal status: Prescription only medicine.<br>Additional risk minimisation measures:<br>• None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• WAY4001 - WAYLIVRA® PASS and Product Registry (final PASS study report is expected by Q4 2028(1 year from end of PASS phase). |
| Use in patients with hepatic impairment | Routine risk minimisation measures:<br>• SmPC section 4.2 and 5.2.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• WAY4001 - WAYLIVRA® PASS and Product Registry (final PASS study report is expected by Q4 2028 (1 year from end of PASS phase) |
| Use in patients with severe renal impairment | Routine risk minimisation measures:<br>• SmPC sections 4.2 and 5.2.<br>• Recommendations for closely observing patients with renal impairment in SmPC section 4.2.<br>• Legal status: Prescription only medicine.<br>Additional risk minimisation measures:<br>• None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• WAY4001 - WAYLIVRA® PASS and Product Registry (final PASS study report is expected by Q4 2028 (1 year from end of PASS phase) |
| Long-term safety | Routine risk minimisation measures:<br>• None.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• WAY4001 - WAYLIVRA® PASS and Product Registry (final PASS study report is expected by Q4 2028 (1 year from end of PASS phase) |

| | | |
|---|---|---|
| Use in elderly | Routine risk minimisation measures:<br>• SmPC sections 4.2, 5.1, and 5.2.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None | Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:<br>• None<br>Additional pharmacovigilance activities:<br>• WAY4001 - WAYLIVRA® PASS and Product Registry (final PASS study report is expected by Q4 2028 (1 year from end of PASS phase) |

Abbreviations: PASS= post-authorisation safety study; PL=Package leaflet; SmPC= Summary of Product Characteristics

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the risk management plan (RMP) for WAYLIVRA. The RMP details important risks of WAYLIVRA, how these risks can be minimised, and how more information will be obtained about WAYLIVRA's risks and uncertainties (missing information).

WAYLIVRA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how WAYLIVRA should be used.

This summary of the RMP for WAYLIVRA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of WAYLIVRA's RMP.

## I. The medicine and what it is used for

WAYLIVRA is authorised for use as an adjunct to diet for the treatment of adult patients with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and triglyceride lowering therapy has been inadequate (see SmPC for the full indication). It contains volanesorsen as the active substance and is given by subcutaneous (SC) injection.

Further information about the evaluation of WAYLIVRA’s benefits can be found in WAYLIVRA’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/waylivra

## II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of WAYLIVRA, together with measures to minimise such risks and the proposed studies for learning more about WAYLIVRA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of WAYLIVRA, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of WAYLIVRA is not yet available, it is listed under 'missing information' below.

## II.A List of Important Risks and Missing Information

Important risks of WAYLIVRA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of WAYLIVRA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

| **List of important risks and missing information** | |
|---|---|
| Important identified risks | Thrombocytopenia<br>Injection site reactions |
| Important potential risks | Immunogenicity<br>Hepatotoxicity<br>Nephrotoxicity |
| Missing information | Use in pregnancy and lactation<br>Use in patients with hepatic impairment<br>Use in patients with severe renal impairment<br>Long-term safety<br>Use in elderly |

## II.B Summary of Important Risks

| **Important Identified Risk: Thrombocytopenia** | |
|---|---|
| Evidence for linking the risk to the medicine | Clinical Studies CS2, CS6, CS7, CS16.<br>CS6 and CS16 are the randomised controlled trials.<br>In the non-clinical study, dose and time-dependent reductions in mean platelet count were observed in monkeys, both in the 3-month (40 mg/kg/wk) and 9-month studies (6 mg/kg/wk). |
| Risk factors and risk groups | Patients with moderate or severe thrombocytopenia (< $100 \times 10^9$/L). |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC section 4.4, 4.8<br>• PL section 4 |

| | |
|---|---|
| | • Recommendations for platelet count monitoring in SmPC sections 4.2, and 4.4 and notification of platelet count monitoring to patients in PL section 2.<br>• Treatment recommendations with volanesorsen in case of low platelet counts in SmPC section 4.2.<br>• Contraindication for initiating the treatment with volanesorsen in patients with thrombocytopenia (platelet count < 140 x $10^9$/L) in SmPC section 4.3 and PL section 2.<br>• Caution advised for the use of volanesorsen in patients deemed at higher risk of thrombocytopenia in SmPC section 4.4 and 4.5.<br>• Recommendation to discontinue antiplatelet medicinal products/NSAIDs/anticoagulants for platelet levels <75 x $10^9$/L and instruction to discontinue at <50 x $10^9$/L in SmPC section 4.4 and 4.5.<br>• Instructions for patients to notify their doctor if they are taking any medications that can lower platelet count or stop the blood from clotting in PL section 2.<br>• Instructions for patients to monitor for and notify their doctors immediately if they experience any signs or symptoms of thrombocytopenia or a serious bleed in SmPC section 4.4 and PL sections 2 and 4.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• HCP guide and Patient/Carer Guide |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry<br>See section II.C.1 of this summary for an overview of the post-authorisation development plan |

Abbreviations: NSAIDs= Nonsteroidal anti-inflammatory drugs; PL=Package leaflet; SmPC= Summary of Product Characteristics

| **Important Identified Risk: Injection site reactions** | |
|---|---|
| Evidence for linking the risk to the medicine | Clinical Studies CS2, CS6, CS16, CS7.<br>CS6 and CS16 are the randomised controlled trials.<br>In non-clinical studies, mononuclear cell infiltrates at the subcutaneous injection site were observed in mice, rats, and monkeys. |
| Risk factors and risk groups | Potential risk factors for injection site reactions: sites where pressure or rubbing may occur from clothing. This medicinal product should not be injected into tattoos, moles, birthmarks, bruises, rashes, or areas where the skin is tender, red, hard, bruised, damaged, burned, or inflamed. |
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC section 4.2 and 4.8 |

| | |
|---|---|
| | • PL section 4<br>• Instructions on the method of administration in Section 4.2 of SmPC.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry<br>See section II.C.1 of this summary for an overview of the post-authorisation development plan |

Abbreviations: PL=Package leaflet; SmPC= Summary of Product Characteristics

| **Important Potential Risk: Immunogenicity** | |
|---|---|
| Evidence for linking the risk to the medicine | Clinical Studies CS2, CS4, CS6, CS16, CS7 and CS17.<br>CS6 and CS16 are the randomised controlled trials. |
| Risk factors and risk groups | There are currently no known specific risk factors for immunogenicity associated with volanesorsen. |
| Risk minimisation measures | Routine risk minimisation measures<br>• SmPC sections 4.4.<br>• PL section 4.<br>• Recommendation to contact Marketing Authorisation Holder to discuss antibody testing, if formation of anti-drug antibodies with a clinically significant effect is suspected in section 4.4 of SmPC.<br>• Recommendation to monitor inflammation through quarterly assessment of erythrocyte sedimentation rate in section 4.4 of SmPC.<br>• Contraindication for initiating the treatment with volanesorsen if the patient is hypersensitive to the active substance or to any of the excipients in section 4.3 of SmPC and PL section 2.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry<br>See section II.C.1 of this summary for an overview of the post-authorisation development plan |

| **Important Potential Risk: Hepatotoxicity** | |
|---|---|
| Evidence for linking the risk to the medicine | Clinical Studies CS2, CS6, CS7, and CS16.<br>CS6 and CS16 are the randomised controlled trials. |
| Risk factors and risk groups | There are no known specific risk factors for elevated transaminases observed during treatment with volanesorsen. Alcohol ingestion, concomitant medications and fatty liver disease may be contributing factors. |
| Risk minimisation measures | Routine risk minimisation measures<br>• SmPC section 4.4.<br>• PL sections 2 and 4.<br>• Recommendation for monitoring hepatotoxicity is included in SmPC section 4.4 and PL section 2.<br>• Caution advised for the use of volanesorsen in patients with any liver problems in PL section 2.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry<br>See section II.C.1 of this summary for an overview of the post-authorisation development plan |

Abbreviations: PL=Package leaflet; SmPC= Summary of Product Characteristics

| **Important Potential Risk: Nephrotoxicity** | |
|---|---|
| Evidence for linking the risk to the medicine | Studies CS2, CS6, CS7, and CS16<br>CS6 and CS16 are the randomised controlled trials. |
| Risk factors and risk groups | There are no known specific risk factors for abnormal renal function tests observed during treatment with volanesorsen.<br>Dehydration, diabetes mellitus and concomitant nephrotoxic medications may be contributing factors. |
| Risk minimisation measures | Routine risk minimisation measures<br>• SmPC section 4.4.<br>• PL sections 2 and 4.<br>• Recommendation for monitoring for nephrotoxicity is included in SmPC section 4.4.<br>• Caution advised for the use of volanesorsen in patients with any kidney problems in PL section 2.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures: |

| | |
|---|---|
| | • None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry<br>See section II.C.1 of this summary for an overview of the post-authorisation development plan |

Abbreviations: PL=Package leaflet; SmPC= Summary of Product Characteristics

| **Missing Information: Use in Pregnancy and Lactation** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC section 4.6<br>• PL section 2<br>• Recommendations to avoid to avoid the use of volanesorsen during pregnancy in SmPC section 4.6 and PL section 2<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry<br>See section II.C.1 of this summary for an overview of the post-authorisation development plan |

Abbreviations: PL=Package leaflet; SmPC= Summary of Product Characteristics

| **Missing Information: Use in Patients with Hepatic Impairment** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC section 4.2 and 5.2.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry<br>See section II.C.1 of this summary for an overview of the post-authorisation development plan |

Abbreviations: PL=Package leaflet; SmPC= Summary of Product Characteristics

| **Missing Information: Use in Patients with Severe Renal Impairment** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures: |

| | |
|---|---|
| | • SmPC sections 4.2 and 5.2<br>• Recommendations for closely observing patients with renal impairment in SmPC section 4.2.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry<br>See section II.C.1 of this summary for an overview of the post-authorisation development plan |

Abbreviations: SmPC= Summary of Product Characteristics

| **Missing Information: Long-term Safety** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry<br>See section II.C.1 of this summary for an overview of the post-authorisation development plan |

| **Missing Information: Use in Elderly** | |
|---|---|
| Risk minimisation measures | Routine risk minimisation measures:<br>• SmPC sections 4.2, 5.1, and 5.2.<br>• Legal status: Prescription only medicine<br>Additional risk minimisation measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry<br>See section II.C.1 of this summary for an overview of the post-authorisation development plan. |

Abbreviations: SmPC= Summary of Product Characteristics

# II.C Post-authorisation Development Plan

## II.C.1 Studies which are Conditions of the Marketing Authorisation

The following studies are conditions of the marketing authorisation:

**Study short name and title**

WAY4001: WAYLIVRA® Post-Authorisation Safety Study and Product Registry

**Rationale and study objectives**

The aim of this study (PASS phase and WAYLIVRA product registry phase) is to further characterise the safety and effectiveness of WAYLIVRA in patients with FCS under real-world conditions.

Primary objective

- To evaluate the safety of WAYLIVRA on severe thrombocytopenia and bleeding in FCS patients according to the dose recommendation and dose algorithm in the SmPC.

Secondary Safety Objectives

- To determine real-world incidence rates of mild, moderate and severe thrombocytopenia, and associated bleeding events, overall and by event grading
- To describe prescribers' adherence to recommendations for platelet monitoring and dose reduction to minimise the risk of thrombocytopenia as outlined in the SmPC
- To determine real-world incidence rates and severity of:
    - immunogenicity/immunological events
    - hepatotoxicity
    - renal toxicity
    - severe injection site reactions
    - mild, moderate and severe thrombocytopenia with or without an associated serious bleeding episode in patients weighing less than 70kg, overall and by event grading.
- To describe the safety profile in the following patient sub-groups for patients treated with WAYLIVRA:
    - patients with hepatic impairment
    - patients with renal impairment
    - elderly patients (≥ 65 years of age)
- To describe the long-term safety profile of WAYLIVRA
- To describe outcomes for WAYLIVRA-exposed pregnancies; specifically, gestational outcomes (e.g., live birth, spontaneous abortion, etc.) and major congenital malformations observed at pregnancy conclusion

Secondary Efficacy Objectives

- To evaluate the long-term efficacy of WAYLIVRA with respect to triglyceride reduction, pancreatitis prevention, and reduction in abdominal pain frequency and severity
- To evaluate the effect of WAYLIVRA on health-related quality of life assessed by FCS-related symptoms and impacts on daily lives

## II.C.2 Other Studies in Post-authorisation Development Plan

None.

## Annex 4 - Specific Adverse Event Follow-up Forms

Thrombocytopenia Questionnaire

Hepatic Adverse Event Questionnaire

Hypersensitivity Questionnaire

Injection Site Reaction Questionnaire

Renal Adverse Event Questionnaire

Constitutional Symptoms Questionnaire

## Annex 6 - Details of Proposed Additional Risk Minimisation Measures

Prior to the launch of Waylivra in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The objective of the programme is to provide information on the risks of thrombocytopaenia and bleeding; advise on platelet monitoring and provide details about the dose frequency adjustment algorithm. The MAH shall ensure that in each Member State where Waylivra is marketed, all healthcare professionals and patients and carers who are expected to prescribe, dispense, use Waylivra have access to/are provided with the following educational package:

- Physician educational material
- Patient information pack

**The physician educational material** should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

**The Guide for healthcare professionals** shall contain the following key elements**:**

- Relevant information on thrombocytopaenia and severe bleeding
- Details of the population at higher risk for thrombocytopaenia and bleeding (e.g. those with weight less than 70 kg), and patients for which Waylivra is contraindicated (i.e. patients with chronic or unexplained thrombocytopaenia)
- Platelet monitoring recommendations including dosage adjustment recommendations, both before and during treatment
- That the patients should be made aware of the possibility of thrombocytopaenia and to seek medical attention immediately in case of signs of bleeding. Patients must be reminded to read the patient leaflet and the patient/carer guide
- Duration of treatment covered by each prescription should be commensurate with, and encourage adherence to, the dosing and monitoring frequency of volanesorsen treatment.
- Information about the FCS disease registry and the PASS study and the importance of contributing to those studies

The **patient information pack** should contain:

- Patient information leaflet
- A patient/carer guide

**The Patient/carer guide** shall contain the following key messages:

- Relevant information on thrombocytopaenia and severe bleeding
- Importance of monitoring platelet levels

- Possible need for dose adjustments or treatment pauses based on platelet test results
- Need to be aware of and alert to the signs of thrombocytopaenia and the importance of seeking immediate assistance from a health professional
- Information about the FCS disease registry and the PASS study and encouragement to participate in those studies
- Reporting of any adverse drug reaction to a health professional