Medicinrådet

Bilag til Medicinrådets vurdering af olezarsen til behandling af familiært chylomikronæmisyndrom (FCS)

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. olezarsen
2. Forhandlingsnotat fra Amgros vedr. olezarsen
3. Ansøgers endelige ansøgning vedr. olezarsen

Sobi's comments on the assessment report for Tryngolza (olezarsen) for the treatment of FCS

Sobi thanks DMC for the thorough assessment of Tryngolza as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).

DMC presents the result of their assessment in two scenarios, Scenario 1 and 2, both with changes to the submitted base case. Sobi believes that the submitted base case best represents the cost-effectiveness of Tryngolza for the treatment of FCS in Denmark and would like to highlight the following changes DMC has made to the submitted base case:

Direct treatment effect of Tryngolza on the risk of developing acute pancreatitis (AP):

In Scenarios 1 and 2, DMC removes the treatment-specific effect of Tryngolza on the risk of developing an AP. In the Balance study, one (1) episode of AP occurred among the 22 patients in the 80-mg olezarsen group, one (1) episode occurred among the 21 patients in the 50-mg olezarsen group, and 11 episodes (in 7 patients) occurred among the 23 patients in the placebo group (mean rate ratio [pooled olezarsen groups vs. placebo], 0.12; 95% CI, 0.02 to 0.66; p=0.0144) [1]. In the model, to derive the treatment effect observed in the trial, calibration factors are used to adjust the rate ratio between the treatment arms. This is done so that the model reflects the observed data and maintains the observed mean rate ratio over the model's time horizon. When DMC removes this, Tryngolza's effect on APs no longer reflects what was observed in the Balance study.

AP-mortality:

In Scenario 1 and 2, DMC changes the risk of an AP being fatal from 9.6% to 4.5%. Sobi believes that DMC is underestimating the risk of an AP event being fatal.

In the submitted base case, the risk of an AP event being fatal was sourced from the assessment report of Waylivra for the treatment of FCS from the Swedish Dental and Pharmaceutical Benefits Agency (TLV). The mortality in AP among patients with FCS was estimated to be around 6% according to the company, which was confirmed by TLV's clinical expert. However, TLV's clinical expert also stated that approximately 10–20% of patients with APs develop a life-threatening condition, with mortality rates of up to 30% [2]. Based on this, a weighted average probability of death following an AP was estimated at 9.6%. The TLV expert statement is supported by a study by Jadev et al, where it is stated that mortality of an AP event can approach 30% for those who develop pancreatic necrosis, infected abscesses, or multiple organ system failure [3]. Sobi believes that this better reflects the probability of an AP being fatal in Denmark.

Comments on DMC's scenarios:

First, DMC assumes patients in Danish clinical practice will initiate treatment at an earlier age than our submitted base case, changing the starting age from 45 to 30 years. Earlier treatment initiation gives patients more time to benefit from the treatment and may therefore increase the potential to prevent or delay FCS-related complications and generate health benefits over the patient's lifetime.

Second, DMC expects patients to remain on treatment for longer than assumed in our submitted analysis. DMC removed the stopping rule applied in our base case, under which patients with an insufficient response after six months discontinued treatment, because DMC expects patients to continue treatment in Danish clinical practice. Furthermore, DMC reduced the assumed

annual treatment discontinuation rate from 9.09% in our base case to 4.5%, reflecting DMC's expectation that long-term discontinuation will be lower than observed during the Balance study. Taken together, removing the stopping rule and lowering the annual discontinuation rate mean more patients are expected to remain on treatment and therefore continue to receive Tryngolza's clinical benefits. This is also consistent with DMC's sensitivity analyses, which show that lower treatment discontinuation yields a greater incremental QALY gain.

Of the two scenarios presented by the DMC, Sobi thinks DMC's Scenario 1 provides the most reasonable alternative to the submitted base case. The only difference between Scenario 1 and 2 is the extrapolation approach, and Sobi consider the extrapolation approach in DMC's Scenario 1 more appropriate than Scenario 2 for representing the expected long-term treatment effect, under the assumption of *more patients remaining on treatment,* following DMCs changes to the submitted base case as presented above. Rather than assuming that patients remain indefinitely in the TG health state reached at 12 months, Scenario 1 allows continued transitions between TG levels based on the transition patterns observed during the first year. DMC's modelling consequently results in more patients treated with Tryngolza reaching the lower TG categories compared with Scenario 2, which in turn delays complications such as acute and chronic pancreatitis and results in greater health gains.

Adherence to diet

Finally, DMC states in their assessment that there is no information available on subjects' adherence to the low-fat diet in the Balance study. DMC argues that this creates uncertainty regarding the extent to which the diet contributed to the observed effects. DMC considers Danish patients to be well-managed, as they expect they will receive close follow-up and dietary counselling from specialised units and clinical dietitians, which may support better adherence to the diet.

Sobi would like to highlight that adherence to the low-fat diet was monitored throughout the trial. Willingness to adhere to a low-fat diet containing ≤ 20 g of fat per day was an inclusion criterion. Furthermore, dietary counselling was initiated at the start of the Diet Stabilisation Period and repeated at regular intervals throughout the Treatment and Follow-up Period. Subjects were also required to complete a daily dietary questionnaire to document FCS symptoms and diet throughout the study period.

References:

1. Stroes, E.S.G., et al., *Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome*. N Engl J Med, 2024.
2. Tandvårds-och läkemedelsförmånsverket (TLV), *Hälsoekonomisk bedömning av Waylivra (volanesorsen)* 2020.
3. Javed, F., et al., *Familial chylomicronemia syndrome: An expert clinical review from the National Lipid Association*. J Clin Lipidol, 2025. **19**(3): p. 382–403.

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30.10.2026

LSC/MBA

Forhandlingsnotat

Dato for vurdering i Medicinrådet	25.11.2026
Leverandør	SOBI
Lægemiddel	Tryngolza (olezarsen)
Ansøgt indikation	Tryngolza som supplement til diæt hos voksne patienter til behandling af genetisk bekræftet familiært chylomikronæmisyndrom (FCS).
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende priser på Tryngolza. Leverandøren har givet to pristilbud, et pristilbud, som er betinget af en anbefaling og et pristilbud som ikke er betinget af en anbefaling. Tryngolza er endnu ikke lanceret i Danmark, men forventes i medicinpriser.dk [redacted].

Tabel 1: Forhandlingsresultat – betinget pris

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Tryngolza	80 mg (1 stk.)	[redacted]	[redacted]	[redacted]

Prisen i Tabel 1 er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Tryngolza, indkøbes Tryngolza til "Forhandlet SAIP" i Tabel 2.

Tabel 2: Forhandlingsresultat – ikke-betinget pris

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Tryngolza	80 mg (1 stk.)	[redacted]	[redacted]	[redacted]

Aftaleforhold

Amgros vil indgå en aftale på Tryngolza. Aftalen gælder fra den [redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der findes aktuelt ingen godkendte farmakologiske behandlingsalternativer til patienter med FCS i Danmark. Den primære behandling består af en stærkt fedtreduceret diæt (20-25 g fedt/dag), samt standard lipidsænkende behandling med fibrater, statiner og omega-3-fedtsyrer, jf. *Medicinrådets vurdering af olezarsen til behandling af familiært chylomikronæmisyndrom (FCS).*

Leverandøren har netop anmodet Medicinrådet om vurdering af Tryngolza på en kommende indikation, svær hypertriglyceridæmi (sHTG).

Tabel 3 viser de årlige lægemiddeludgifter ved behandling med Tryngolza.

Tabel 3: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Tryngolza	80 mg (1 stk.)	80 mg en gang månedligt, s.c.	[redacted]	[redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
Sverige	Ikke vurderet	Link til status
England	Anbefalet	Link til vurdering

Opsummering

Amgros vil indgå en aftale på Tryngolza med forventet aftalestart
[redacted]

Submission for the Assessment of Tryngolza® (olezarsen) as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS)

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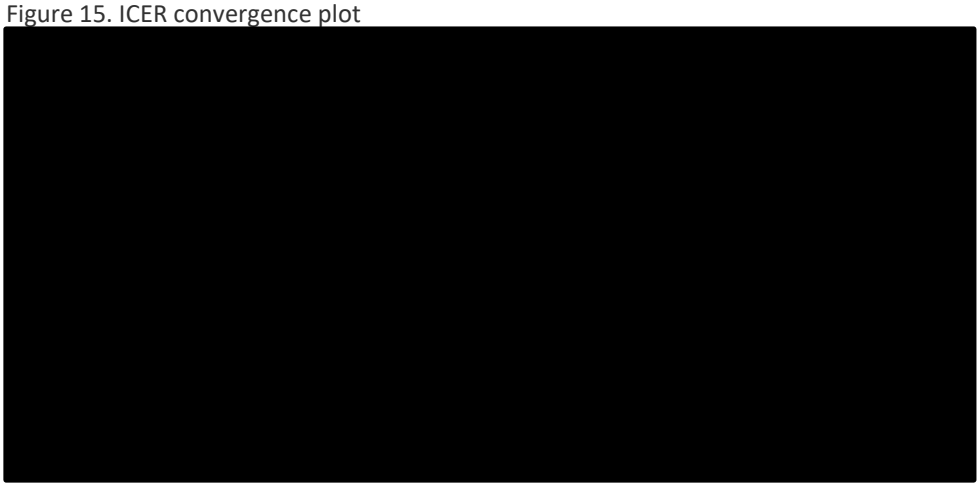
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Abbreviations

Abbreviation	Explanation
AE	Adverse events
AP	Acute pancreatitis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CP	Chronic pancreatitis

CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	Emergency room
FAS	Full analysis set
FCS	Familial chylomicronemia syndrome
HCRU	Healthcare resource utilisation
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
HTG	Hypertriglyceridemia
JCA	Joint Clinical Assessment
LPL	Lipoprotein lipase
LSM	Least-squares mean
MI	Multiple imputation
PGIC	Patient Global Impressions of Change
PROMIS	Patient-Reported Outcome Measurement Information System
PSA	Probabilistic sensitivity analyses
RDI	Relative dose intensity
SAE	Serious adverse event
SmPC	Summary of product characteristics
SoC	Standard of care
TEAE	Treatment-emergent adverse event
TRL	TG-rich lipoproteins
UACR	Urine albumin to creatinine

VLDL	Very low-density lipoproteins

1. Information on the Drug

Drug information	
Trade name	Tryngolza®
Generic name	Olezarsen
Indication as formulated by the European Medicines Agency (EMA)	Tryngolza® is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).
Marketing Authorisation Holder in Denmark	Swedish Orphan Biovitrum AB (publ).
ATC code	C10AX
Combination therapy and/or concurrent treatment	No
Expected date of EU approval (marketing authorisation)	17/09/2025
Has the drug received a conditional marketing authorisation?	No
Has the drug undergone 'accelerated assessment' at EMA?	No
Has the drug received orphan drug designation?	Yes, Tryngolza® was designated an “orphan medicine” on the 21st of August 2024.
Other indications approved by EMA	No
Other indications assessed by the Danish Medicines Council	No
Joint Nordic Assessment (JNHB): **Is current treatment practice comparable across the Nordic countries (DK, FI, IS, NO, SE)?**	**Yes.** There are no official guidelines for the treatment of FCS in Denmark. Assumptions in Denmark are instead based on international guidelines.
Joint Nordic Assessment (JNHB): **Is the drug suitable for a joint Nordic assessment?**	No, as Tryngolza® has already been submitted for reimbursement in other Nordic countries.
Has a Joint European Assessment (JCA) been conducted under EU HTA Regulation?	No

Dispensing	BEGR
Packaging – types, pack sizes/number of units, and strengths	Pack size of one pre-filled pen. Each single-dose pre-filled pen contains 80 mg olezarsen in 0.8 mL solution.

2. Summary Table

Overview	
Indication relevant to the assessment	Tryngolza® is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS). No deviations from the EMA indication have been made.
Dosage regimen and route of administration	The recommended dose of olezarsen is 80 mg administered by subcutaneous injection once monthly.
Choice of comparator	The comparator is no addition to the standard of care (SoC).
Prognosis with current standard treatment (comparator(s))	Current treatment for FCS patients is limited to low-fat diet recommendations and lipid-lowering medications. Despite treatment, patients progress in their disease resulting in increased TG levels and number of acute pancreatitis (AP) [1]. Further, AP can lead to chronic pancreatitis (CP) and increased mortality [2-5]. Elevated TGs alone, without considering pancreatitis history, have also been shown to be associated with an increased risk for mortality [6-8].
Type of documentation for the clinical evaluation	The Phase 3, head-to-head, placebo-controlled Balance Study (NCT04568434) [1, 9].
Main outcomes including at least one outcome for health-related quality of life (difference/improvement compared with comparator(s))	The percentage of fasting TG levels from baseline to six months was −43.5 percentage points (p= 0.0002) between 80 mg olezarsen and placebo, and -22.37 percentage points (p= 0.0044) between 50 mg olezarsen and placebo. Number of AP episodes by week 53: 80 mg olezarsen: 1 episode, 50 mg olezarsen: 1 episode, and placebo: 11 episodes (mean rate ratio [pooled olezarsen groups vs. placebo], 0.12; p=0.0144). The Patient-Reported Outcome Measurement Information System (PROMIS) 29+2 Profile was administered to assess HRQoL. The results did not identify differences from baseline compared with placebo in the olezarsen 80 mg group or the olezarsen 50 mg group. Patient Global Impressions of Change (PGIC) at 6 months: olezarsen 80 mg; 15/19 patients (78.9%), and placebo group;

	9/22 (40.9%). The odds ratio of 80 mg versus placebo was 4.86 (95 CI: 1.08, 21.90).
Serious adverse events for the intervention and comparator	Serious adverse events (AEs) occurred in 14%, 19%, and 39% of patients in the 80 mg olezarsen group, 50 mg olezarsen, and placebo groups, respectively. Pancreatitis was the most reported serious AE across all three groups: placebo (17.4%), olezarsen 50 mg (4.8%), and olezarsen 80 mg (4.5%). Acute pancreatitis was reported in 13% in the placebo group and 0% in both olezarsen groups. Pancreatitis necrotizing was reported in 8.7 % of the placebo group and 0% in both olezarsen groups.
Type of health economic analysis	A cost-utility analysis.
Health economic model	A Markov model is used to assess the cost-effectiveness of Tryngolza® + standard of care (SoC) vs no addition to SoC.
Outcomes and data sources used to extrapolate patient transitions	TG levels and the risk of experiencing an AP, with a history of two or more AP, were based on the Balance study [1]. The risk of an AP for naïve individuals or those with a history of one previous AP episode was estimated from the CALIBER study [6]. The probability of developing CP was estimated from a study by Yadav and colleagues [10]. CP is assumed to incur an excess risk of mortality relative to general population mortality, this was sourced from Nøjgaard et al. [11]. The probability of developing diabetes is estimated using exponential models from the CALIBER study [6].
Instrument and data sources for health-related quality of life	Patient-Reported Outcomes Measurement Information System (PROMIS) and the Patient Global Impression of Change (PGIC) were used in the Balance study [9].
Life-years gained (discounted, half-cycle corrected, and adjusted for background mortality)	[redacted]
QALYs gained (discounted, half-cycle corrected, and adjusted for background mortality)	[redacted]
ICER (DKK/QALY) (discounted, half-cycle corrected, and adjusted for background mortality)	[redacted]
Applicant's assessment of uncertainty	The analysis acknowledges uncertainties inherent in modelling a rare disease.

3. Patient Population, Intervention, Choice of Comparator(s) and Outcome(s)

3.1 Patient Population

3.1.1 The Disease

3.1.1.1 Disease overview

FCS is a rare and severe genetic disorder [12], with literature-based global prevalence estimates of approximately 1–2 in 1,000,000 individuals [13, 14]. In clinical terms, FCS is a severe form of hypertriglyceridemia (HTG), a condition defined by elevated fasting TG levels [15].

FCS first presents in childhood or early adulthood, although symptom onset can also occur during later life [5, 12, 16]. Consistent with this variability, age at diagnosis ranges widely across the literature [5, 16]. In a previous phase 3 clinical trial in patients with FCS, age at diagnosis (n=46) ranged from the immediate postnatal period (<1 year) to 75 years of age (median 27 years) [16].

Lipoprotein Lipase (LPL) is an essential enzyme involved in the clearance of chylomicrons, which are large TG-rich lipoproteins (TRLs) that transport dietary fat from the intestines to other organs and tissues in the body [17, 18]. Diet is the primary exogenous, and the liver is the primary endogenous source of TGs [17, 18]. FCS is caused by mutations affecting the LPL pathway, most commonly in LPL gene or in genes required for LPL function and activity, such as *GPIHBP1*, *APOC2*, *APOA5*, and *LMF1* [12, 19, 20]. These mutations impair LPL activity, leading to markedly elevated plasma TG levels, often ≥10 mmol/L (≥880 mg/dL), compared with normal TG levels of <1.7 mmol/L (<150 mg/dL) [16, 19]. In FCS, plasma TGs are predominantly carried in chylomicrons, which accumulate in plasma [5, 16, 19, 21]. Despite a fasting period of 12-14 hours, circulating chylomicrons persist in patients with FCS, whereas in individuals with normal metabolism, chylomicrons are typically cleared within 3-4 hours after eating [17].

Accumulation of TG-rich lipoproteins (primarily chylomicrons) in plasma underlies a broad spectrum of disease manifestations and a substantially increased risk of acute pancreatitis (AP), chronic pancreatitis (CP), and fatal complications [4, 5]. Episodes of AP often require hospitalisation and can result in organ failure and death [3-5, 22]. Elevated TG levels themselves are associated with increased all-cause mortality [6-8].

The elevated TG levels are associated with debilitating chronic manifestations affecting physical, cognitive, and emotional domains. Patients with FCS experience a broad spectrum of signs and symptoms, including eruptive xanthomas (small yellow papules caused by very high blood TGs), abdominal pain, cognitive symptoms (e.g., concentration

difficulties and brain fog), lipemia retinalis (a milky appearance of the retinal vessels without associated visual impairment), and enlargement of the liver and spleen (hepatosplenomegaly) [3, 5, 17, 23-26]. Some patients experience metabolic comorbidities, such as diabetes [4, 5].

Abdominal pain can be especially detrimental for patients with FCS. In a global survey of lipidologists reporting clinical outcomes in patients with FCS (n=251), 57% of patients experienced recurrent abdominal pain, and nearly one-fifth (17%) experienced abdominal pain requiring hospitalisation (not diagnosed as AP) [4]. The high prevalence of abdominal pain among patients with FCS was further reflected in the IN-FOCUS survey (n=166), in which patients were asked to rate the frequency and severity of physical symptoms associated with FCS; abdominal pain was the most commonly reported symptom, affecting 41% of patients [5].

Overall, FCS exerts a substantial negative impact on patients' health-related quality of life (HRQoL), including emotional health and psychological well-being, ability to perform daily activities of living, and family life and personal relationships [5, 27].

FCS patients are treated by lipidologists in Denmark.

3.1.1.2 Acute and chronic pancreatitis

AP is an inflammatory condition of the pancreas that can trigger both local pancreatic effects and broader systemic inflammation. Clinical presentation ranges from mild disease to severe episodes complicated by pancreatic necrosis, organ failure, and mortality [28]. Hypertriglyceridemia-induced AP is highly morbid and associated with intensive care unit admission, prolonged hospitalisation, and up to 8% in-hospital mortality [22, 29].

HTG, a condition defined as elevated TG levels, is a well-established cause of AP [15, 30]. FCS is characterised by severe HTG (sHTG), with TG levels ≥10 mmol/L (≥880 mg/dL), and the risk of AP is even higher in FCS than in other types of sHTG [31]. Patients with FCS have been shown to have a 23-fold higher risk of AP compared with patients with other forms of sHTG (with TG levels of approximately 5-9 mmol/L (450–800 mg/dL)) [32]. Across cohort studies, 40–76% of patients with FCS have been reported to experience AP episodes [3-5, 16, 31, 33]. In the survey of lipidologists, 67% of patients reported experiencing an episode of AP requiring hospitalisation; half had multiple hospitalisations for recurrent AP (2–96 hospitalisations), and one-third required intensive care [4]. Even after a single episode, AP can lead to long-term complications (e.g., CP), and AP-related mortality is as high as 6% in patients with FCS [4, 11, 22].

Recurrent AP can lead to long-term complications such as CP, pancreatic tissue damage, pancreatogenic (type 3c) diabetes, and pancreatic insufficiency [2-5]. The Copenhagen Pancreatitis Study, a prospective study of Copenhagen residents with AP or CP and approximately 30-year follow-up by Danish registries (n=352), found that nearly one quarter of patients (24%) with a first attack of AP progressed to CP [11]. Notably, the mortality rate of patients with AP that progressed to CP was 2.7 times higher than for

patients who did not progress to CP, and approximately 5.3-6.5 times higher than the general population [11].

To summarise, FCS is a rare, severe genetic disorder characterised by markedly elevated fasting TG concentrations (≥10 mmol/L or ≥880 mg/dL) that drive the disease's most serious complications. Elevated TGs are a well-established cause of AP and, in FCS, confer a 23-fold higher risk of AP compared with other forms of severe hypertriglyceridemia [32]. The high TG burden also underlies the substantial impairment in HRQoL reported by patients, which is largely attributable to TG-related symptoms such as abdominal pain, fatigue, and frequent hospitalisations [4, 5]. Consequently, TG reduction is a central therapeutic target for preventing AP and improving patients' overall well-being.

3.1.2 Unmet need.

Currently available treatments for FCS, i.e., TG-lowering therapies and dietary management strategies, have limitations [5, 16, 27, 34, 35]. TG-lowering therapies are ineffective and do not reduce AP risk in patients with FCS because these treatments often target the LPL-dependent pathway, which is non-functional in this disease [16, 17, 31, 34, 35]. Extreme dietary restrictions, such as adhering to a low-fat diet (10-20g of fat per day), remain the current mainstay of FCS treatment; however, even with adherence, patients with FCS still experience clinical manifestations of their disease, including extremely high TGs and episodes of AP [5, 25, 34-36]. Therefore, an unmet need remains for an FCS treatment that can effectively decrease TG levels, alleviate symptoms (including abdominal pain), reduce the risk of AP, demonstrate a favourable safety profile, and minimise the burden of disease management [5, 34, 37].

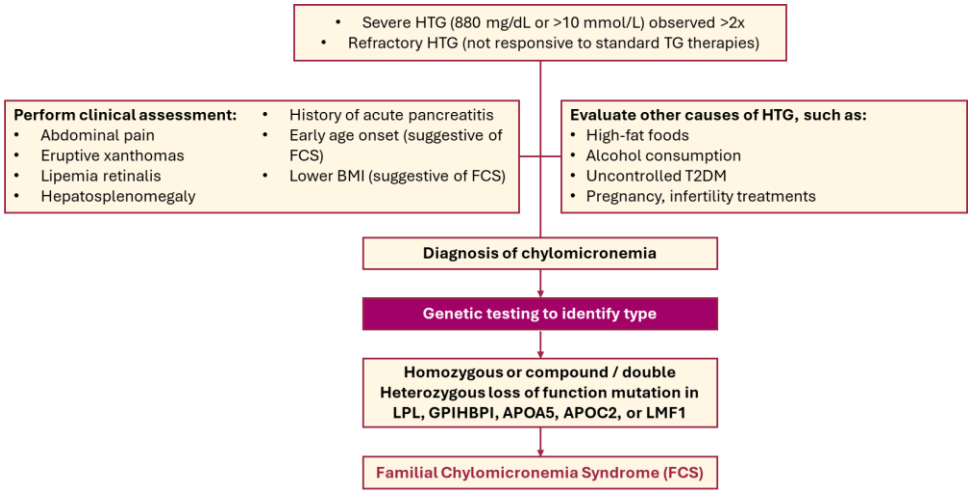
3.1.3 Selected patient population

The patient population relevant to this application is: adult patients who are genetically confirmed to have FCS, according to the EMA indication [38]. The population is consistent with the population of the pivotal Balance trial [1]. No interventions for the treatment of FCS have been previously assessed by the DMC. Figure 1 describes the key steps in the identification and diagnosis of chylomicronemia, followed by FCS.

Incidence data for FCS are scarce in the published literature; therefore, prevalence-based estimates were used to estimate the number of patients with FCS in Denmark. Global prevalence of FCS is estimated to be approximately 1–2 in 1,000,000 individuals [13, 14], which correspond to 6-12 patients in Denmark. Based on a Danish clinical expert, there are approximately [redacted] patients with FCS in Denmark [39]. The approved indication for Tryngolza® only includes adult patients, which means the paediatric population is excluded. In Denmark, this corresponds to approximately one-fifth of the population being under 18 years of age, reducing the potentially treatable population to around [redacted] patients. Furthermore, treatment discontinuations observed in clinical studies are considered, where approximately [redacted] (corresponding to approximately [redacted] patient in Danish clinical practice) discontinue treatment. Furthermore, not all adult patients with genetically confirmed FCS are expected to initiate treatment Tryngolza®. Some patients have triglyceride levels and disease burden that are considered

sufficiently controlled with current dietary management and therefore may not be considered in need of pharmacological treatment. In addition, some patients may decline treatment, may not meet the clinician's threshold for initiating lifelong therapy, or may have clinical circumstances that make treatment inappropriate. In summary, the final eligible patient population is assumed to be [redacted]. A gradual increase in uptake in expected, as Tryngolza® would be the first approved treatment for this patient population. Uptake is assumed to grow over time as clinicals gain greater familiarity and experience with the treatment.

Figure 1. Identification and Diagnosis of Chylomicronemia



APOA5, apolipoprotein A-V; APOC2, apolipoprotein C-II; BMI, body mass index; FCS, familial chylomicronemia syndrome; GPIHBP1, glycosylphosphatidylinositol anchored high-density lipoprotein-binding protein 1; HTG, hypertriglyceridemia; LMF1, lipase mutation factor 1; LPL, lipoprotein lipase; MCS, multifactorial chylomicronemia syndrome; T2DM, type 2 diabetes mellitus; TG, triglyceride.

Adapted from Hegele et al. 2020 [35] and Moulin et al. 2018 [12]

Table 1. Expected number of patients and patient uptake of the intervention

	2026	2027	2028	2029	2030
Expected number of patients* (prevalence)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient uptake**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

*The number of patients in Denmark eligible for the new treatment in accordance with the EMA indication, minus the number of patients who are not considered suitable for treatment (e.g., due to age or comorbidity), and minus those who are expected to decline treatment. As a general rule, the number of new (incident) patients per year should be used. However, if prevalent patients are expected to be offered treatment, these should be included in year 1. **Patient uptake is defined relative to the expected number of eligible patients. If full patient uptake (100%) is not expected from year 1 due to a gradual implementation, the relevant percentage uptake must be specified for each year. Once the new treatment is expected to be fully implemented, patient uptake must reach 100% (no later than year 5). For definitions of patient numbers and patient uptake, see the Danish Medicines Council's guideline on budget impact analysis.

3.2 Intervention

Tryngolza® is an antisense oligonucleotide-triantennary N-acetylgalactosamine (GalNAc3) conjugate that causes degradation of apolipoprotein C3 (apoC-III) messenger ribonucleic acid (mRNA) through selective binding to its mRNA. This results in specific reductions of serum apoC-III protein leading to plasma triglyceride reductions. Studies suggest that apoC-III regulates both triglyceride metabolism and hepatic clearance of chylomicrons and other triglyceride-rich lipoproteins [38]. An overview of the intervention, including its mechanism of action is presented in Table 2.

The average dose of olezarsen in the Balance study is [redacted], which corresponds to 80 mg olezarsen multiplied by the compliance rate [redacted] of the olezarsen 80 mg treatment group [9]. The dose distribution corresponds to 100% to 80 mg olezarsen. In the trial, one (4.5%) patient had a dose reduction, i.e., experienced a dose reduction from 80 mg once every 4 weeks to 50 mg every 4 weeks due to [redacted] [9]. The patient received the [redacted] of olezarsen 80 mg on [redacted], after which the patient experienced [redacted]. The patient recovered from the events of [redacted] on the [redacted], but did not receive the [redacted] dose, as there was discussion about the patient having a dose reduction. No treatment was reported for the events. On [redacted], the patient restarted olezarsen and received her [redacted] at the reduced dose of 50 mg. After, the patient experienced [redacted]. The patient did not receive treatment for the events. The patient recovered from the event of [redacted] on [redacted] and the patient recovered from the events of [redacted] on [redacted]. Treatment with olezarsen was permanently discontinued due to these events [9].

The dose of Tryngolza® expected to be used in the Danish clinical practice is the approved one by EMA corresponding to 80 mg. Thus, no dose reductions are expected in clinical practice [38].

Table 2. Overview of the intervention

Therapeutic indication relevant to the assessment	Tryngolza® is indicated as an adjunct to diet in adult patients for the treatment of genetically confirmed familial chylomicronemia syndrome (FCS).
Generic name	Olezarsen
ATC code	C10AX
Mechanism of action	Olezarsen is an ASO-GalNAc3 conjugate that causes degradation of apoC-III mRNA through selective binding to its mRNA. This results in specific reductions of serum apoC-III protein leading to plasma triglyceride (TG) reductions.

Route of administration	Subcutaneous use.
Packaging type, pack sizes, shelf life, and strengths	Pack size of one pre-filled pen. Each single-dose pre-filled pen contains 80 mg olezarsen in 0.8 mL solution. The shelf life is 4 years.
Package size(s)	One pre-filled pen.
If vials: Can these be shared?	No
Pre-medication: Is premedication required? If yes, specify which	No
Co-administration: Is the drug to be administered with other drugs? If yes, specify which	No
Need for diagnostics, monitoring, or other tests (e.g., *companion diagnostics*)	Yes, genetic test to confirm FCS diagnosis.

Table 3. The intervention in the clinical study and in the health economic model

	Clinical study	Health economic model
Dosage and frequency	50 mg or 80 mg of olezarsen once every 4 weeks for 49 weeks.	80 mg once monthly until treatment discontinuation
Average dose	[redacted], which corresponds to 80 mg olezarsen multiplied by the compliance rate [redacted]% of this treatment group.	As per clinical trial
Criteria for treatment discontinuation	Pregnancy, withdrawal of consent, experiencing an AE that requires permanent discontinuation or unblinding, laboratory test abnormalities meeting any of the stopping rules described in the protocol.	The model combines the Markov structure with a short-term decision tree. The decision tree allows for a response assessment in which patients discontinue Tryngolza® if there has not been a sufficient reduction in TG levels at 6 months (either a 25% reduction from baseline or TG levels below 2,000 mg/dL). This is consistent with the Summary of Product Characteristics (SmPC), which states that some patients may not respond to treatment after 6 months. In such cases, discontinuation of

	Clinical study	Health economic model
		Tryngolza® should be considered on an individual basis by the prescribing physician [38]. In the model, the annual discontinuation rate of [redacted] is applied, based on [redacted] patients that discontinued treatment with olezarsen 80 mg in the trial.
Treatment duration	50 mg olezarsen: median of 365.0 days and mean of 339.3 days. 80 mg olezarsen: median of 364.0 days and mean of 323.4 days.	Average time on treatment (years): [redacted]
Dose adjustment: Specify whether/how dose adjustments are applied*	Dose adjustments, and/or decreasing the dose frequency was allowed for safety or tolerability after consultation with the Medical Monitor. Dose adjustments should not occur unless absolutely necessary prior to the primary analysis time point (Month 6).	The model includes a compliance rate of [redacted]% for Tryngolza® as described in section 3.2.
Treatment interruption: Specify whether/how treatment interruptions (pause) are applied*	Dose interruptions were allowed for safety or tolerability after consultation with the Medical Monitor.	The model includes a compliance rate of [redacted]% for Tryngolza® as described in section 3.2

*If Relative Dose Intensity (RDI) is used to account for dose adjustments and/or treatment interruptions, include a definition of RDI. See the Danish Medicines Council's guideline for calculating costs.

3.2.1 The Intervention in the Context of Danish clinical practice

There are currently no national guidelines for the treatment of FCS in Denmark, which was confirmed by a Danish clinical expert [39]. However, according to information at medicin.dk [40], the primary treatment of FCS is a severely fat-reduced (20-25 g/day) diet, which represents SoC for this patient population. These recommendations are aligned with input from a Danish clinical expert, who recommends a very low-fat diet, alcohol abstinence, and physical activity [39].

In relation to the current Danish clinical practice, and in the absence of pharmacological treatments available for patients with FCS, it is believed that Tryngolza® will be considered as an adjunct treatment to SoC.

Patients with FCS will only be given Tryngolza® if the disease is confirmed by genetic testing.

3.2.2 Advanced Therapy Medical Products

Not applicable.

3.3 Choice of Comparator(s)

The treatment recommendation for FCS in Denmark is a fat-reduced diet, alcohol abstinence, and physical activity (see Section 3.2.1), which is considered as SoC. In this assessment, the most relevant comparator to Tryngolza® is no addition to SoC.

It should also be noted Redemplo® (plozasiran) received marketing authorisation from the European Commission on 19 June 2026 as an adjunct to diet to reduce triglyceride levels in adult patients with familial chylomicronemia syndrome (FCS) [41]. However, plozasiran is not recommended for use in Denmark by DMC and is not considered to be a part of Danish SoC. Therefore, it is not considered to be a relevant comparator to Tryngolza®.

Table 4. Overview of the comparator

Overview	
Therapeutic indication relevant to the assessment	N/A
Generic name	N/A
ATC code	N/A
Mechanism of action	N/A
Route of administration	N/A
Packaging type, pack sizes, shelf life, and strengths	N/A
Package size(s)	N/A
If vials: Can these be shared?	N/A
Pre-medication: Is premedication required? If yes, specify which	N/A

Overview	
Co-administration: Is the drug to be administered with other drugs? If yes, specify which	N/A
Need for diagnostics, monitoring, or other tests (e.g., *companion diagnostics*)	N/A

Table 5. Comparator in the clinical study and in the health economic model

	Clinical study	Health economic model
Dosage and frequency	Placebo: matching volume to olezarsen, e.g., SC injection every 4 weeks, adjunct to a fat-reduced diet.	A fat-reduced diet. Triglyceride-lowering medication (statins, omega-3 fatty acids, and fibrates) were allowed in the Balance study and are therefore included in the model.
Average dose	N/A	N/A
Criteria for treatment discontinuation	Pregnancy, withdrawal of consent, experiencing an AE that requires permanent discontinuation or unblinding, laboratory test abnormalities meeting any of the stopping rules described in the protocol.	N/A
Treatment duration	Median of 364.0 days and mean of 353.1 days.	N/A
Dose adjustment: Specify whether/how dose adjustments are applied*	N/A	N/A
Treatment interruption (pause): Specify whether/how treatment interruptions are applied*	Dose interruptions were allowed for safety or tolerability after consultation with the Medical Monitor.	Not included in the cost calculations.

	Clinical study	Health economic model
Dosage and frequency [if weight-based, specify body weight in parenthesis and any criteria for switching to a flat dose]	N/A, no addition to SoC	N/A

*If Relative Dose Intensity (RDI) is used to account for dose adjustments and/or treatment interruptions, include a definition of RDI. See the Danish Medicines Council's guideline for calculating costs.

Abbreviations: SC; subcutaneous; SoC: standard of care, AEs: adverse events.

3.4 Subsequent Treatment

N/A. Patients with FCS are expected to receive lifelong treatment of Tryngolza® in addition to SoC, as FCS is a chronic condition.

Table 6. Assumptions regarding subsequent treatment in the health economic analysis (N/A)

	[Intervention] %	[Comparator] %	Mean treatment duration (incl. source)	Dosage (dose, frequency and route of administration, incl. source)	Any assumptions regarding dose adjustments and treatment interruptions, incl. source)
N/A	N/A	N/A	N/A	N/A	N/A

3.5 Relevant Outcomes

3.5.1 Definition of Outcomes

The most relevant outcomes are reductions in TG levels and the number of APs.

Table 7. Outcomes

Outcome	Follow-up time point	Definition
Percent change in fasting TG from baseline to month 6	Month 6	The difference between the olezarsen groups and the placebo group in the percent change in the fasting triglyceride level from baseline to 6 months 6 months was defined as the average of weeks 23, 25, and 27.

Outcome	Follow-up time point	Definition
Included in Balance study		The primary analysis was performed by treatment group: first in the olezarsen 80 mg group, then in the olezarsen 50 mg group.
Percent change in fasting TG from baseline to month 12 Included in Balance study	Month 12	The difference between the olezarsen groups and the placebo group in the percent change in the fasting triglyceride level from baseline to 12 months 12 months was defined as the average of weeks 51 and 53. The analysis was performed in the olezarsen 80 mg group, and in the olezarsen 50 mg group.
Adjudicated AP event rate from week 1 to week 53 – LSM event rate	Week 53	The incidence rate of AP was adjudicated by a blinded, independent committee according to Atlanta Classification [42].

Abbreviations: LSM, least-squares mean.

Source: Stroes et al. 2024 [1].

3.5.2 Relevance of Outcomes

As described in section 3.1.1, an accumulation of TG lipoproteins in plasma substantially increases the risk of AP, CP, and death [4, 5]. Episodes of AP often require hospitalisation and intensive care and can result in persistent organ failure and mortality [3-5, 22]. Elevated TG levels themselves, without accounting for pancreatitis-related outcomes such as AP and CP, are associated with an increased all-cause mortality [6-8].

Additionally, high chylomicron levels are known to trigger AP [43]. The risk of AP increases by 3% to 4% with each incremental increase of 100 mg/dL in TG levels [44]. EMA refers to that any decrease in fasting TG levels, even within a limited timeframe, is expected to reduce the risk of AP in patients with FCS [43].

This evidence highlights the relevance of the outcome percentage change in fasting TG from baseline for this application. Additionally, the decrease in AP rate is associated with an increase in patients' HRQoL [39].

3.5.3 Validity of Outcomes

In the Balance study, the main outcomes were fasting TG levels and adjudicated AP. Fasting TGs are an objective laboratory outcome measured under standardised fasting conditions. AP is a clinically relevant outcome in FCS and, in Balance, APs were adjudicated by an independent blinded committee according to the revised Atlanta classification, supporting outcome validity [42]. A Danish clinician confirmed that the outcomes were valid for Denmark [39].

4. Health Economic Analysis

4.1 Reference-case Assumptions

Table 8. Reference-case assumptions in the health economic analysis

	Assumption	Justification
Patient population	Adult patients with genetically confirmed FCS	The relevant patient population for the assessment
Intervention	Tryngolza® (olezarsen) 80 mg once per month	The intervention being assessed
Comparator(s)	No addition to SoC	Standard treatment of the condition. SoC consists of a strict fat-reduced diet.
Clinical outcomes	Reduction in TG levels AP events Developing CP Developing diabetes Mortality	AP and CP are clinically relevant outcomes for patients with FCS. Elevated TG levels are associated with an increased risk och AP and CP, and Tryngolza® lowers TG levels [9]. AP and CP are also associated with an increased risk of mortality [4, 11]
Type of analysis	Cost-utility	Treatment with Tryngolza® is assumed to affect both costs and health outcomes compared with current SoC, and therefore a cost-utility analysis is appropriate.
Type of model	Markov model	To capture the natural history of the disease, a Markov model with health states defined by TG levels and history of AP is used.
Mean age at model entry	45 years	Mean age of the Balance trial [1]
Time horizon	Life-time horizon, corresponding to approximately 55 years	FCS is a chronic condition; thus, cost-effectiveness will be assessed over a life-time horizon.
Cycle length	3 months	The model cycle length is 13 weeks, corresponding to

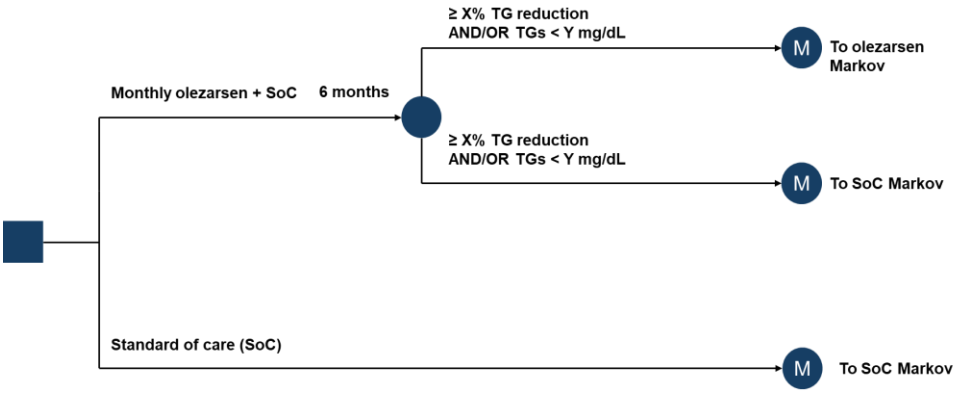
	Assumption	Justification
		approximately 3 months. This is aligned with the model structure used for Waylivra® (volanesorsen), in the treatment of FCS, which has been accepted for decision-making by both TLV and NICE. 13 weeks is also assumed to be long enough to capture relevant resource use and clinical changes.
Half-cycle correction	Yes	As per DMC guidelines [45]

4.2 Model Type and Model Structure

FCS is a rare and chronic disease characterised by severely elevated TG levels, leading to an increased risk of significant clinical complications such as AP, CP, and death [3-5, 17, 23-26]. Thus, to assess the cost-effectiveness of Tryngolza® + SoC vs SoC alone, a Markov model will be used with health states defined by TG level, history of AP and mortality, to reflect the natural history of the disease. The model structure has been previously accepted in HTA assessments of FCS [46, 47]

The model combines the Markov structure with a short-term decision tree (Figure 2).The decision tree allows for a response assessment in which patients discontinue Tryngolza® if there has not been a sufficient reduction in TG levels at 6 months (either a 25% reduction in TG levels from baseline or TG levels below 2,000 mg/dL). This is consistent with the Summary of Product Characteristics (SmPC), which states that some patients may not respond to treatment after 6 months. In such cases, discontinuation of Tryngolza® should be considered on an individual basis by the prescribing physician [38].

Figure 2. Decision tree



Abbreviations: SoC, Standard of care; TG, Triglyceride

The Markov model (Figure 3) consists of 12 mutually exclusive health states based on TG level, history of AP and mortality, and one health state for CP and one for death. Patients enter the model in a health state corresponding to their fasting TG levels and AP history. Each health state is associated with a risk of AP, with higher levels of TG and a previous history of AP being related to an increased risk of AP, CP, and death. The three categories of AP-history are:

1. AP naïve (no documented history of AP)
2. 1 AP (one previous AP event)
3. Recurrent AP (at least two previous AP events)

These categories of AP history are considered to be relevant for capturing the disease progression and risk of AP events. A study using these definitions found the incidence of AP to increase with a greater history of AP events [48].

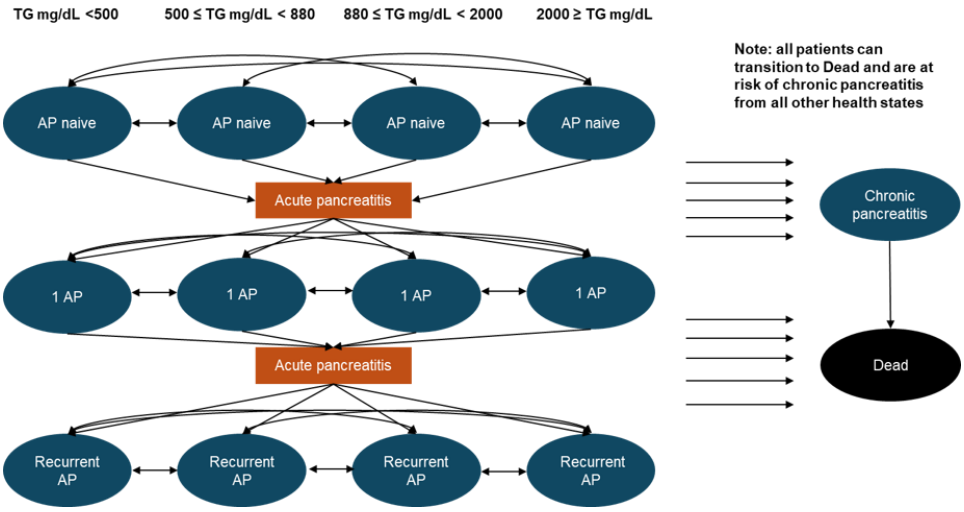
The health states are also based on TG level categories to reflect the increased risk of AP, CP, and mortality associated with increasing TG levels. Each patient's TG value at each model time point is allocated to one of four TG categories:

1. TG <500 mg/dL
2. TG ≥500 mg/dL and <880 mg/dL
3. TG ≥880 mg/dL and <2,000 mg/dL
4. TG ≥2,000 mg/dL

As described in section 3.1.1, recurrent AP can lead to long-term complications such as CP and pancreatogenic (type 3c) diabetes [2-5]. CP in the model is captured as an absorbing health state in which patients have gained irreversible damage to the pancreas, which can develop because of AP in all health states. The risk of CP is predicted by previous number of AP events, and the risk is independent of treatment arm. Thus, CP is driven by health state occupancy. Diabetes is captured as a co-morbidity in the health states, with prevalence determined by both the TG category and the patient's AP history, as both higher TG levels and past AP events are known to increase risk of diabetes [2].

In addition to death from natural causes, excess mortality is estimated using published evidence on mortality associated with AP, and CP. In the model, Tryngolza® is assumed to have an indirect treatment effect on mortality associated with AP, as AP risk is much higher in the presence of high TGs [49] and Tryngolza® reduces TG levels [1].

Figure 3. Markov model



Abbreviations: AP, Acute pancreatitis; SoC, Standard of care; TG, Triglyceride

Table 9. Choice of health economic analysis, model, and model structure

Type of health economic analysis	Type of model	Model structure	Assumptions
Cost-utility analysis	Markov model	12 health states based on AP history (AP naïve, 1 AP, recurrent AP) and TG levels (<500 mg/dL, ≥500 mg/dL and <880 mg/dL, ≥880 mg/dL and <2,000 mg/dL, ≥2,000 mg/dL). The model also includes one health state for CP and one for death.	Patients transitioning from Tryngolza® to SoC (due to treatment discontinuation for any reason) are assumed to remain in their health state for the remaining part of the time horizon. After 12 months, patients are assumed to remain in their health state for the remaining part of the time horizon. The 13 health states defined by TG levels and AP history are assumed to drive clinically meaningful sequalae for the patient population.

5. Literature Review

5.1 Literature Used to Assess Clinical Effectiveness and Safety

Since the clinical assessment is exclusively informed by the head-to-head study Balance, the literature search for efficacy and safety studies was omitted. The relevant literature included in the assessment of efficacy and safety is presented in Table 10.

Table 10. Relevant literature included in the assessment of effectiveness and safety

Reference	Study name	NCT number	Study dates (start date and expected end date, data cut-off, and expected data cut-offs)	Used for comparison of*
Erik S.G. Stroes, M.D., Ph.D., Veronica J. Alexander, et al. Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. The new England journal of medicine. 2024; 390:1781-92 [1] Data on file: Clinical Study Report (CSR) Balance trial. 2024 [9] Tryngolza® Assessment report (EPAR) [43]. ClinicalTrials.gov: A Study of Olezarsen (Formerly Known as ISIS 678354 and AKCEA-APOCIII-LRx) Administered to Patients With Familial Chylomicronemia Syndrome (FCS) (BALANCE) (NCT04568434). 2025 [50]	Balance	NCT04568434	Start: 18/11/20 End: 17/10/23 Completion and data cut-off: 14/07/23	Tryngolza®+ SoC compared to Placebo+ SoC for the effectiveness, safety, and HRQoL outcomes of adult patients with FCS.

5.2 Literature Used to Assess Health-Related Quality of Life

Table 11. Relevant literature included in the assessment of health-related quality of life

Reference	Instrument and purpose	Identification method (documented in appendix)	Used in section
Matza et al. Estimating health state utilities associated with a rare disease: familial chylomicronemia syndrome (FCS). Journal of Medical Economics. 2020; 23(9): 978-984. [51]	Health state vignettes to estimate utility based on AP history and TG levels.	Commissioned study	Section 10.3

5.3 Literature Used as Input in the Health Economic Model

In the Balance trial, no subjects that were AP naïve or had had 1 prior AP had an AP event, therefore, the risk of developing an AP event for patients in the AP naïve and 1 AP health states were derived from external literature. Further, since the Balance trial only followed patients for one year, external data was used for long-term comorbidities such as CP, diabetes and mortality. The external data was identified through a targeted literature search.

Table 12. Relevant literature used in the health economic model

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in section
Erik S.G. Stroes, M.D., Ph.D., Veronica J. Alexander, et al. Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. The new	Change in TG levels for all patients and incidence of AP for recurrent AP patients.	Clinical trial of the assessed intervention.	Section 9.3

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in section
England journal of medicine. 2024; 390:1781-92 [1]			
Patel R, P.L., Soran H. et al.. Elevated plasma triglyceride concentration and risk of adverse clinical outcomes in 1.5 million people: a CALIBER linked electronic health record study. Cardiovascular Diabetology. 2022: **21**(102) [6]	The incidence of acute pancreatitis events.		Section 9.3
Yadav D OCM, P.G. Natural history following the first attack of acute pancreatitis. The American Journal of Gastroenterology. 2012; **107**(7): pp. 1096–103. [52]	The incidence of chronic pancreatitis.		Section 9.3
Javed F, Hegele RA, Garg A, et al. Familial chylomicronemia syndrome: An expert clinical review from the National Lipid Association. *J Clin Lipidol*. 2025;19(3):382-403. doi:10.1016/j.jacl.2025.03.013 [34]	Probability AP is fatal		Section 9.3
Gaudet, D., et al. (2016). Acute Pancreatitis is Highly Prevalent and	Probability AP is fatal		Section 9.3

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in section
Complications can be Fatal in Patients with Familial Chylomicronemia: Results From a Survey of Lipidologist. National Lipid Association Journal of Clinical Lipidology. **10**: pp**.** 680–681. [4]			
Nojgaard, C., et al. (2011). Progression from acute to chronic pancreatitis: prognostic factors, mortality, and natural course. Pancreas **40**(8): pp. 1195–1200. [11]	Average SMR of chronic pancreatitis		Section 9.3
Publicly available data.	Medicine costs, medicine administration, management of health events and comorbidities.	Sourced from medicinpriser.dk [53], Catalogue for estimating unit costs (Værdisætning af enhedsomkostninger [54]), Danish DRG costs from Sundhedsdatastyrelsen [55], physician visit tariffs from læger.dk	Section 10.3.4

6. Clinical Studies

6.1 Tryngolza® in addition to SoC Compared with no addition to SoC in patients with FCS

6.1.1 Relevant Studies

The main source of clinical evidence for patients with FCS treated with olezarsen is the pivotal study Balance (NCT04568434), which was a phase 3, randomised, multicentre, double-blind, placebo-controlled study [1, 9] (Table 13). It aimed to measure the efficacy and safety of olezarsen 80 mg or olezarsen 50 mg in addition to SoC compared with placebo in addition to SoC in patients with FCS. All the patients were instructed to consume no more than 20 g of total fat per day, and alcohol use was discouraged during the trial. The trial enrolled 66 patients, and it was conducted during the years 2020-2023 in Canada, the US, the EU, and the UK.

The primary efficacy analysis was conducted in the full analysis set (FAS), which included all the patients who had undergone randomisation and received at least one dose of olezarsen or placebo. The latest data cutoff corresponding to the end of treatment is 14th of July 2023. This is the data cutoff for all the results presented in this application.

A total of 66 patients were randomly assigned to treatment. Forty-three patients were treated with at least 1 dose of olezarsen (22 patients in the olezarsen 80 mg group, 21 in the olezarsen 50 mg group), and 23 patients were treated with placebo [1]. All patients in each group received the treatment to which they were randomised [9].

Six (9.1%) patients discontinued study drug (3 [13.6%] patients in the olezarsen 80 mg group, 2 [9.5%] patients in the olezarsen 50 mg group, and 1 [4.3%] patient in the placebo group) [1]. Two (9.1%) patients in the olezarsen 80 mg group and 1 (4.8%) patient in the olezarsen 50 mg group discontinued study drug due to an AE; no patients in the placebo group discontinued treatment due to an AE [1]. The other two patients treated with olezarsen that discontinued treatment (one in the 50 mg and one in the 80 mg) was due to voluntary withdrawal. The main reason for treatment discontinuation of the patient in the placebo group was due to Investigator judgment.

The treatment-emergent adverse events (TEAEs) that led to permanent discontinuation of study drug in the 80 mg group were moderate and nonserious TEAEs. The single discontinuation in the olezarsen 50 mg group was caused by the serious adverse event (SAE) of sudden death, which was assessed by the Investigator as unlikely related to study drug [1].

The Balance trial is described in detail in Appendix A.

Table 13. Overview of study characteristics for all studies included in the comparison

Study name, NCT number (reference)	Studio design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
Balance study, NCT04568434 [1, 9]	Phase 3, randomised, multicentre, double-blind, placebo-controlled study.	An approximately 4-week, but no more than 8-week, screening period (which included an at-least-2-week diet stabilization/run-in period for patients not already on a stable diet and an approximately 2-week qualification period). Followed by a 53-week treatment period during which study drug was administered as a once-every-4-	Patients with fasting triglyceride levels of 880 mg/dL (10 mmol/L) or higher and genetically confirmed FCS.	Olezarsen (subcutaneous administration), 50 or 80 mg every 4 weeks for 49 weeks of the 53-week treatment period.	Olezarsen-matching placebo (subcutaneous administration), every 4 weeks for 49 weeks of the 53-week treatment period.	Primary Endpoint: • Percent Change in Fasting TG from Baseline to Month 6 for 50 and 80 mg olezarsen compared to placebo, Secondary Endpoints: • Percent Change in Fasting TG from Baseline to Month 12 for 50 and 80 mg olezarsen compared to placebo. • Percent Change in Fasting apoC-III from Baseline to Month 6 and to Month 12 for 50 and 80 mg olezarsen compared to placebo. • Proportion of Patients who Achieve ≥ 40% Decrease in Fasting TG from Baseline to Month 6 for 50 and 80 mg compared to placebo. • Percent Change in Fasting apoB-48 from Baseline to Month 6 and to Month 12 for 50 and 80 mg compared to placebo. • Percent Change in Fasting non-HDL-C from Baseline to Month 6 and to Month 12 for 50 and 80 mg compared to placebo. • Adjudicated AP Event Rate from Week 1 to Week 53 for total 50 and 80 mg compared to placebo(Prior History of Pancreatitis ≤ 10 years prior to Screening) – LSM Event Rate. • Adjudicated AP Event Rate from Week 1 to Week 53 for total 50 and 80 mg compared to placebo – LSM Event Rate, • Adjudicated AP Event Rate from Week 13 to Week 53 for total 50 and 80 mg compared to

Study name, NCT number (reference)	Studio design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
		week (i.e., Week 1 through Week 49). Followed by a 13-week post-treatment evaluation period or transition to open-label extension (OLE) study (NCT05130450).				placebo (Prior History of Pancreatitis ≤ 10 years prior to Screening) – LSM Event Rate. • Adjudicated AP Event Rate from Week 13 to Week 53 for total 50 and 80 mg compared to placebo – LSM Event Rate, • Proportion of Patients who Achieve ≥ 70% Decrease in Fasting TG from Baseline to Month 6 for 50 and 80 mg compared to placebo. • Proportion of Patients who Achieve Fasting TG ≤ 880 mg/dL at Month 6 for 50 and 80 mg compared to placebo. • Adjudicated AP Event Rate from Week 1 to Week 53 for total 50 and 80 mg compared to placebo(in patients with ≥ 2 Events in 5 Years Prior to Enrollment) – LSM Event Rate • Adjudicated AP Event Rate from Week 13 to Week 53 for total 50 and 80 mg compared to placebo (in patients with ≥ 2 Events in 5 Years Prior to Enrollment) – LSM Event Rate • Proportion of Patients who Achieve fasting TG ≤ 500 mg/dL at Month 6 for 50 and 80 mg compared to placebo. Month 6 was defined as the average of Weeks 23, 25, and 27, and Month 12 was defined as the average of Weeks 51 and 53.

6.1.2 Comparability of Studies

Not applicable since the application is based on the head-to-head study Balance.

6.1.2.1 Comparability of Patients Across Studies

A total of 60 patients (91%) of the 66 randomly assigned to the trial group completed the assigned trial regimen. The majority of the patients were female, white, and had a normal body-mass index, and the mean (±SD) triglyceride level was 2630±1315 mg /dL (29.7±14.9 mmol/L). Of the 66 patients, 55 (83%) had biallelic pathogenic variants in LPL, and the remaining 11 (17%) had other biallelic causative genotypes. The patients were generally representative of the population of patients with this rare disease in the United States, Canada, and Europe. At screening, 47 patients (71%) had a recorded history of AP within the previous 10 years, and 26 (39%) had previously received volanesorsen. The mean number of previous episodes of AP across the trial groups ranged from 4.1 to 6.6 during the previous 10 years, with a maximum of 79 episodes in one patient [1]. The baseline characteristics of patients included in the Balance study are presented in Table 14.

Table 14. Patients' baseline characteristics in included studies used in the comparative analysis of effectiveness and safety

	Balance		
	Olezarsen, 80 mg (n = 22)	**Olezarsen, 50 mg (n = 21)**	**Placebo (n = 23)**
Age, years	47.7±13.3	43.2±12.1	44.0±14.7
Sex, no. (%)			
Female	11 (50)	15 (71)	12 (52)
Male	11 (50)	6 (29)	11 (48)
Race and ethnic group, no. (%)†			
White	17 (77)	17 (81)	22 (96)
Hispanic or Latino	1 (5)	3 (14)	3 (13)
Asian	3 (14)	3 (14)	0
Native Hawaiian or Pacific Islander	0	1 (5)	0
Other	2 (9)	0	1 (4)

	Balance		
	Olezarsen, 80 mg (n = 22)	Olezarsen, 50 mg (n = 21)	Placebo (n = 23)
Weight, kg	68.4±16.7	61.2±11.6	67.8±16.1
Body-mass index‡	25.1±6.0	22.4±3.5	24.2±4.1
History of AP in the previous 10 years, no. (%)	17 (77)	15 (71)	15 (65)
No. of episodes of AP per patient in the previous 10 years§	4.8±7.5	4.1±4.4	6.6±16.5
Type 1 or 2 diabetes mellitus, no. (%)	7 (32)	3 (14)	6 (26)
Hypertension, no. (%)	4 (18)	3 (14)	6 (26)
Tobacco user, no. (%)	2 (9)	3 (14)	0
Current thrombocytopenia, no. (%)¶	2 (9)	4 (19)	4 (17)
Laboratory measures, mg/dL			
Triglyceride level			
Mean	2613±1499	2684±1235	2596±1256
Median (range)	2086 (683-6898)	2679 (779-5965)	2493 (334-5436)
Apolipoprotein C-lll level	27.5±11.6	27.7±10.5	27.7±11.7
Total cholesterol level	277.4±99.3	323.4±100.5	286.0±113.9
LDL cholesterol level	22.8±14.1	17.6±8.5	16.7±8.4
HDL cholesterol level	14.5±4.5	15.7±4.0	14.7±3.8
Total apolipoprotein B level	58.4±17.2	65.2±13.5	59.7±18.9
Apolipoprotein B-48 level	11.6±8.1	18.5±15.3	14.2±14.2

	Balance		
	Olezarsen, 80 mg (n = 22)	Olezarsen, 50 mg (n = 21)	Placebo (n = 23)
Chylomicron triglyceride level	2477±2123	2302±1265 ‖	2269±1237
Chylomicron-C level plus VLDL cholesterol level**	245.7±110.9	293.2±103.1	255.3±114.4
Non-HDL cholesterol level	262.9±100.4	307.6±101.8	271.3±113.3
Previous treatment with volanesorsen, no. (%)	8 (36)	8 (38)	10 (43)
Concomitant medications, no. (%)			
Statin	5 (23)	4 (19)	7 (30)
Omega-3 fatty acid	12 (55)	6 (29)	7 (30)
Fibrate	11 (50)	8 (38)	11 (48)
Other lipid-lowering agent	3 (14)	0	3 (13)

Note: Plus-minus values are means ± SD. To convert the values for cholesterol to millimoles per litre, multiply by 0.02586. To convert the values for triglycerides to millimoles per litre, multiply by 0.01129. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, VLDL very low-density lipoprotein.

† Race and ethnic group were reported by the patients. Patients could report both a race and an ethnic group.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ The numbers of previous episodes of pancreatitis were obtained from the medical records; episodes were not adjudicated for patients older than 5 years of age. One patient in the placebo group had a history of 79 episodes of acute pancreatitis. Without this patient, the mean number of acute pancreatitis episodes in the previous 10 years in the placebo group is 3.3±4.9.

¶ Thrombocytopenia was defined as a platelet count lower than 140,000 per cubic millimetre.

‖ Data on the chylomicron triglyceride level were available for 20 patients in the 50-mg olezarsen group.

** This variable represents the cholesterol content in the density fraction of less than 1.006 g per millilitre and represents the combined cholesterol content of the chylomicron and VLDL fractions.

Source: Stroes et al. 2024 [1].

6.1.3 Comparability of Study Population(s) with Danish Patients Eligible for Treatment

The characteristics and inputs used in the health economic model compared with the ones from the Balance study population and from the Danish patients eligible for treatment are presented in Table 15. The inputs used in the health economic model are based on the Balance trial.

Table 15. Characteristics of the relevant Danish population and input parameters in the health economic model*

	Danish population (source)	Study population (Balance study) [1]	Health economic model (based on Balance study) [1]
Age, years	Assumed same as Balance	Olezarsen, 80 mg = 47.7±13.3 Olezarsen, 50 mg = 43.2±12.1 Placebo = 44.0±14.7	45
Sex (male), no. (%)	Assumed same as Balance	Olezarsen, 80 mg = 11 (50) Olezarsen, 50 mg = 6 (29) Placebo = 11 (48)	Male = 42.4%

*Plus-minus values are means ± SD.

6.1.4 Analysis Method

For the three endpoints presented in the application (see section 3.5) the FAS population was used for the analyses. No supplementary presentations (e.g., subgroup and sensitivity analyses) were included in this application. The method used for each analysis of the Balance study data is described in Appendix A.

More specifically, for the three endpoints presented in this application, the following analysis methods were used:

- Percent change in fasting TG from baseline to month 6: an ANCOVA model in the FAS population was used. The ANCOVA model included the effects of treatment (olezarsen 80 mg, olezarsen 50 mg, or Placebo), 2 randomization stratification factors (history of pancreatitis and previous treatment with volanesorsen), and log-transformed baseline TG. To account for potential heterogeneity in variance, the 95% CI of the treatment differences were calculated using the robust variance estimator based on the Bell and McCaffrey method. If patients had intercurrent event(s) before Week 23, e.g., treatment discontinuation, use of additional medication, changes in background or concomitant treatments, the Treatment Policy strategy was implemented, the patients' assessments post intercurrent events were continued to be collected and utilized in the analysis. Patients with a missing TG value after discontinuation had TG value multiply imputed at Primary analysis time point based on the known assessments from the retrieved dropouts (i.e., patients who discontinue before Week 23 but still have TG assessments at Week 23, 25 or 27), if there was a sufficient number of retrieved dropouts. The imputation model included the following variables: TG values at baseline and post-baseline

visits and the 2 randomization stratification factors. The multiple imputation was stratified by treatment group. If there was not a sufficient number of retrieved dropouts, missing TG value at the primary time point was imputed using a “wash-out” (Jump to Reference, J2R) multiple imputation approach. With the approach, patients treated with olezarsen who discontinue study had missing post-discontinuation TG values multiply imputed based on the fasting TG at Baseline, 2 randomization stratification factors, and the imputation model for the placebo group. Patients in the placebo group who discontinued the study had missing post-discontinuation TG values multiply imputed based on fasting TG values at Baseline and post-baseline visits from the placebo group.

- Percent change in fasting TG from baseline to month 12: the same analysis method as for the primary analysis of the primary endpoint presented above was used.
- Adjudicated AP event rate from week 1 to week 53 in the FAS: the adjudicated AP event rates were compared between pooled olezarsen treatment group and placebo group using a Poisson regression model or Negative Binomial regression model with the treatment group, history of pancreatitis (yes/no), previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated AP events in 5 years prior to the enrollment as a covariate. The logarithm of time in years that each patient observed during the corresponding analysis period (Week 13 to Week 53 or Week 1 to Week 53/ET) was used as an offset variable.

The number and proportion of patients with missing measurements for each outcome reported in this application are the following:

- Per cent change in fasting TG from baseline to month 6: placebo ([redacted]), olezarsen 50 mg ([redacted]), olezarsen 80 mg ([redacted]) [9].
- Percent change in fasting TG from baseline to month 12: placebo ([redacted]), olezarsen 50 mg ([redacted]), olezarsen 80 mg ([redacted]) [9].
- Adjudicated AP event rate from week 1 to week 53 in the FAS: there were no patients with missing measurements for this outcome.

6.1.5 Effect – Results per Study (Balance)

The efficacy results relevant for this application correspond to the per cent change in fasting TG from baseline to month 6 and to month 12, and the adjudicated AP event rate from week 1 to week 53, which are presented below. More detailed results for these endpoints are presented in Appendix B. The data cutoff for the efficacy results is the 14th of July 2023. The results presented in this application are consistent with those presented in the EMA's scientific discussion (EPAR), no discrepancies are reported here.

6.1.5.1 Per cent change in fasting TG from baseline to month 6 and to month 12

The efficacy results showed that the difference between the 80-mg olezarsen group and the placebo group in the per cent change in the fasting TG level from baseline to 6 months was significant, with a least-squares mean reduction of 43.5 percentage points (95% confidence interval [CI], -69.1 to -17.9; p<0.001) (Figure 4) [1]. Absolute values for these results are shown in Figure 5 [1].

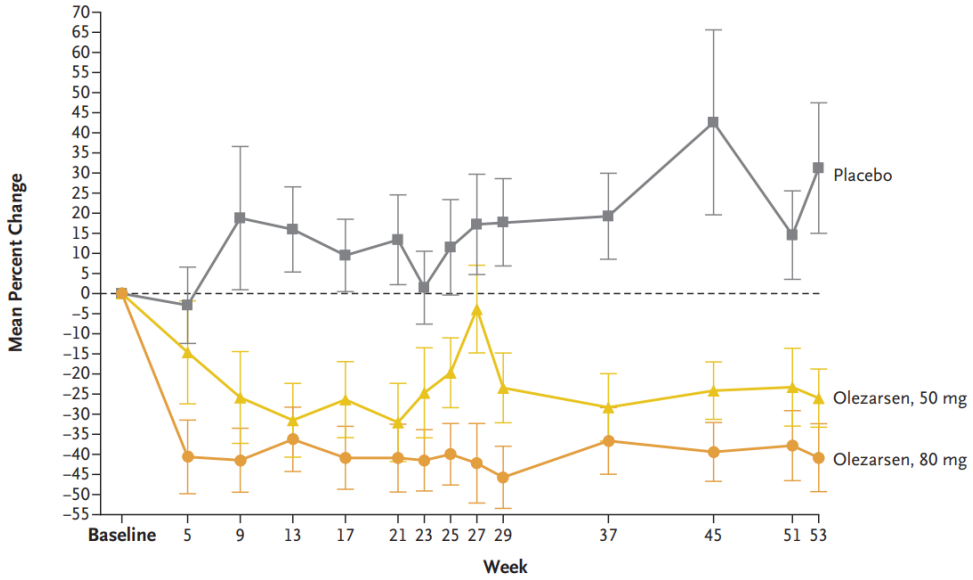
The result of the second primary endpoint, which was the same as the first one but comparing between the 50-mg olezarsen group and the placebo group, was not significant (least-squares mean change, -22.4 percentage points [95% CI, -47.2 to 2.5]; p=0.08) (Figure 4) [1].

Fasting TG levels continued to decrease through month 12 for both the olezarsen 80 mg and olezarsen 50 mg groups, with a placebo-adjusted mean per cent change from baseline of -59.4% (95% CI: -90.7, -28.1; p=0.0002) for the olezarsen 80 mg group and -43.8% (95% CI: -73.9, -13.7; p=0.0044) for the olezarsen 50 mg group [1, 9].

Mean per cent (Figure 4) and absolute (Figure 5) changes in TG levels from baseline over time demonstrated a consistent lowering effect during the 12-month treatment period.

In the EPAR of olezarsen published by EMA [43], it is stated that overall, the results of the lipid profile in the treated patients at Month 6 and 12 might be considered clinically relevant compared with placebo.

Figure 4. Mean per cent change from baseline in fasting plasma levels of triglycerides over time

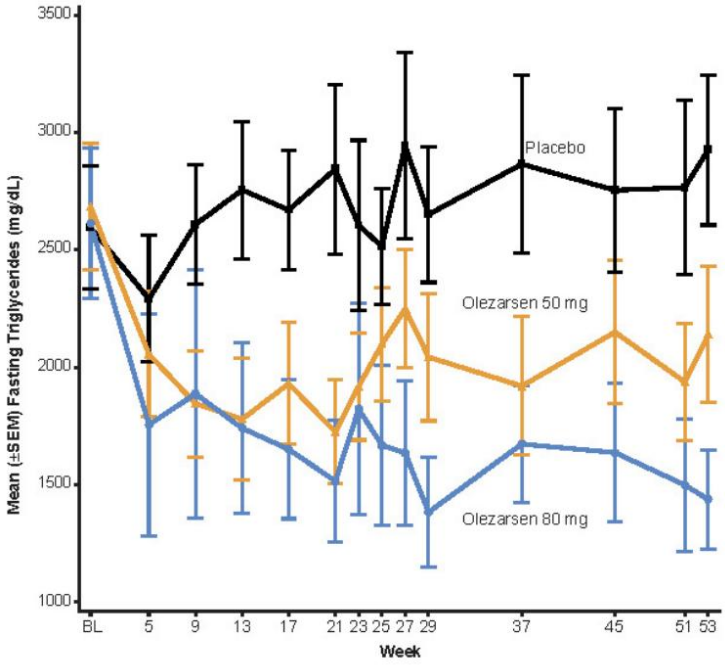


No. of Patients													
Placebo	23	23	21	21	22	22	19	21	19	21	22	20	19	20
Olezarsen, 50 mg	21	19	18	20	19	15	17	19	18	18	18	19	18	19
Olezarsen, 80 mg	22	21	20	21	20	20	15	19	16	20	18	19	15	17

Note: Shown are the mean per cent changes from baseline in fasting plasma levels of triglycerides over time in the full analysis set. Error bars denote standard errors.

Source: Stroes et al. 2024 [1].

Figure 5. Mean absolute plasma fasting triglyceride levels



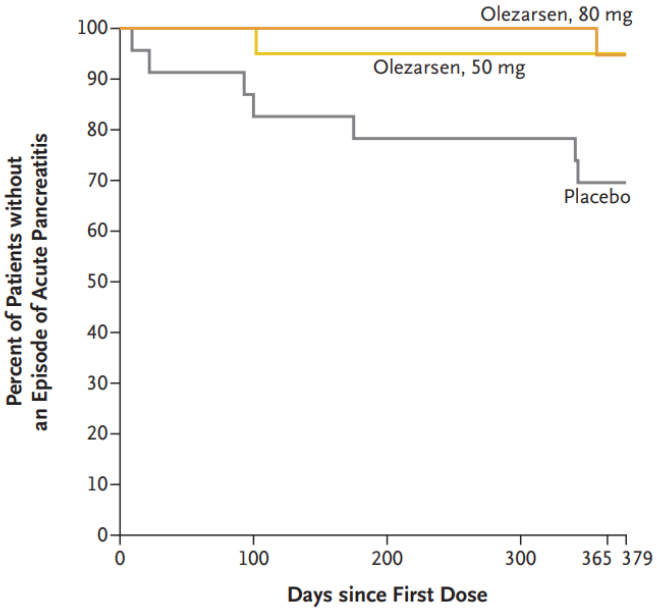
Abbreviations: SEM, standard error of the mean

Source: Stroes et al. 2024 [1].

6.1.5.2 Adjudicated acute pancreatitis event rate from week 1 to week 53 – LSM event rate

By week 53, 1 episode of AP occurred among the 22 patients in the 80-mg olezarsen group, 1 episode occurred among the 21 patients in the 50-mg olezarsen group, and 11 episodes (in 7 patients) occurred among the 23 patients in the placebo group (mean rate ratio [pooled olezarsen groups vs. placebo], 0.12; 95% CI, 0.02 to 0.66; p=0.0144) [1, 9]. All 9 patients who had an episode of AP had had two or more previous episodes before the trial. Kaplan–Meier curves for the time to the first episode of AP are shown in Figure 6. The first episode of pancreatitis occurred on day 357 in the 80-mg olezarsen group, day 102 in the 50-mg olezarsen group, and day 9 in the placebo group [1].

Figure 6. Kaplan–Meier curves for the time to the first episode of acute



No. at Risk					
Placebo	23	19	18	18	14 5
Olezarsen, 50 mg	21	20	19	19	17 5
Olezarsen, 80 mg	22	20	20	19	18 9

Note: The last observation at week 53 (day 365) included a visit window up to day 379.

Source: Stroes et al. 2024 [1].

In the EPAR of olezarsen, it is stated that based on the results from the Balance study, the decrease in fasting TG levels reduces the rate of AP and that high chylomicron levels are known to trigger AP [43]. The risk of AP increases by 3% to 4% with each incremental increase of 100 mg/dL in TG levels [44]. Consequently, EMA acknowledges that any decrease in fasting TG level, even within a limited timeframe, is expected to reduce the risk of pancreatitis in patients with FCS. Additionally, EMA considers that the reduction in the rate of AP is clinically relevant.

7. Comparative Analyses N/A

This section is not applicable since the application is based on the head-to-head study Balance.

7.1 Analysis Method

Not applicable.

7.2 Results of the Comparative Analysis

Not applicable.

Table 16. Results from the comparative analysis of [intervention] vs. [comparator] in [patient population] (N/A)

Outcome	[Intervention] (N = x)	[Comparator] (N = x)	Result
N/A	N/A	N/A	N/A

7.3 Effect – Results per [Outcome]

Not applicable

8. Safety

Adverse events described in this section are considered treatment-emergent adverse events (TEAEs). All TEAEs were coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0 [9]. The safety set population was used for all safety analyses, this population is defined as all patients who were randomized and received any dose of olezarsen or placebo [9]. The severity of AEs and SAEs relating to laboratory tests were graded based on criteria from the common terminology criteria for adverse events (CTCAE) Version 5.0, November 2017, and the severity of AEs and SAEs relating to AEs at the injection site were graded based on criteria from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007 [9]. Any other AE was graded mild (the event is easily tolerated by the patient and does not affect the patient's usual daily activities), moderate (the event causes the patient more discomfort and interrupts the patient's usual daily activities), and severe (the event is incapacitating and causes considerable interference with the patient's usual daily activities). An overview of the adverse events that occurred during the treatment period are presented in Table 17.

The most common adverse events were coronavirus disease 2019, abdominal pain, and diarrhoea, none of which occurred more frequently among the patients who received either dose of olezarsen than among those who received placebo. SAEs occurred in 14% of the patients in the 80-mg olezarsen group, in 19% of those in the 50-mg olezarsen group, and in 39% of those in the placebo group. No SAEs were related to the trial drug. Adverse events of moderate severity that were considered to be related to the trial drug or placebo occurred in 4 patients (18%) in the 80-mg olezarsen group: 1 patient had chills, myalgia, and trismus; 1 had chest discomfort, diarrhoea, flushing, and vomiting; 1 had a transient decrease in the platelet count; and 1 had alopecia. Three patients (2 in the 80-mg olezarsen group and 1 in the 50-mg olezarsen group) reported adverse events (diarrhoea, vomiting, chest discomfort, chills, myalgia, trismus, and flushing) that led to treatment discontinuation. One death occurred in the 50-mg olezarsen group, and this death was assessed by the investigator as being unrelated to the trial treatment. Injection-site reactions were reported in 14% of the patients in the 80-mg olezarsen group, 14% of those in the 50-mg olezarsen group, and 9% of those in the placebo group; all of these injection-site reactions were mild [1].

There were no imbalances among the three trial groups with respect to liver, renal, or clinically meaningful platelet laboratory variables [1].

Table 17. Overview of adverse events that occurred during the treatment period [1]

	Olezarsen, 80 mg (N = 22)	Olezarsen, 50 mg (N = 21)	Placebo (N = 23)	Difference, %-points (80 mg vs placebo)	Difference, RR (95% CI) (80 mg vs placebo)	Difference, %-points (50 mg vs placebo)	Difference, RR (95% CI) (50 mg vs placebo)
All adverse events (AE), n (%)	19 (86)	18 (86)	22 (96)	-10	0.90 (0.75, 1.09)	-10	0.90 (0.75, 1.07)
Serious AE (SAE), n (%)[1]	3 (14)	4 (19)	9 (39)	-25	0.36 (0.11, 1.15	-20	0.49 (0.18, 1.34)
AE grade ≥ 3, n (%)[2]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dose reduction due to AE, n (%)	1 (4.5)	0	0	4.5	-	0	-
Treatment discontinuation due to AE, n (%)	2 (9)	1 (5)	0	9	-	5	-

AE = adverse event; CI = confidence interval; RR = risk ratio; SAE = serious adverse event. [1]See ICH definition. [2]Severe AEs reported in the Balance study representing grade ≥ 3 AEs. Sources: Stroes et al. 2024 [1], and Balance CSR, data on file (2024) [9].

All TEAEs with a frequency of ≥ 10%, regardless of grade/severity reported in the Balance study are reported in Table 18. Since not all adverse events were graded according to CTCAE in the Balance study, the SAEs that occurred in ≥ 3% in at least one treatment arm are presented in Table 18.

Table 18. Proportion of patients with adverse events [9]

	Olezarsen 80 mg (N = 22)		Olezarsen 50 mg (N = 21)		Placebo (N = 23)	
	All[1], n patients (%)	**Grade ≥ 3 or SAE[2], n patients (%)**	**All[1], n patients (%)**	**Grade ≥ 3 or SAE[2], n patients (%)**	**All[1], n patients (%)**	**Grade ≥ 3 or SAE[2], n patients (%)**

	Olezarsen 80 mg (N = 22)		Olezarsen 50 mg (N = 21)		Placebo (N = 23)	
Gastrointestinal disorders						
Abdominal pain	4 (18.2)	N/A	3 (14.3)	N/A	8 (34.8)	N/A
Diarrhoea	2 (9.1)	N/A	1 (4.8)	N/A	6 (26.1)	N/A
Gastric varices	-	0	-	0	-	1 (4.3)
Gastric varices haemorrhage	-	0	-	0	-	1 (4.3)
Gastritis	-	0	-	0	-	1 (4.3)
Intestinal perforation	-	1 (4.5)	-	0	-	0
Pancreatitis	1 (4.5)	1 (4.5)	2 (9.5)	1 (4.8)	4 (17.4)	4 (17.4)
Pancreatitis acute	0	0	0	0	3 (13.0)	3 (13.0)
Pancreatitis necrotizing	-	0	-	0	-	2 (8.7)
General disorders and administration site conditions						
Fatigue	1 (4.5)	N/A	1 (4.8)	N/A	4 (17.4)	N/A
Sudden death	-	0	-	1 (4.8)	-	0
Hepatobiliary disorders						
Cholangitis	-	0	-	0	-	1 (4.3)
Hepatic cirrhosis	-	1 (4.5)	-	0	-	0
Infections and infestations						
COVID-19	3 (13.6)	N/A	6 (28.6)	N/A	8 (34.8)	N/A
Cellulitis	0	0	0	0	3 (13.0)	1 (4.3)

	Olezarsen 80 mg (N = 22)		Olezarsen 50 mg (N = 21)		Placebo (N = 23)	
Gastroenteritis bacterial	-	0	-	1 (4.8)	-	0
Influenza	1 (4.5)	N/A	3 (14.3)	N/A	2 (8.7)	N/A
Urinary tract infection	1 (4.5)	N/A	3 (14.3)	N/A	0	N/A
Injury, poisoning and procedural complications						
Intentional overdose	-	0	-	1 (4.8)	-	0
Investigations						
Platelet count decreased	3 (13.6)	N/A	1 (4.8)	N/A	1 (4.3)	N/A
Metabolism and nutrition disorders						
Hypoglycaemia	-	0	-	0	-	1 (4.3)
Hyponatraemia	-	0	-	0	-	1 (4.3)
Pancreatogenous diabetes	-	0	-	0	-	1 (4.3)
Musculoskeletal and connective tissue disorders						
Arthralgia	1 (4.5)	N/A	3 (14.3)	N/A	0	N/A
Pain in extremity	3 (13.6)	N/A	2 (9.5)	N/A	1 (4.3)	N/A
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Squamous cell carcinoma of the oral cavity	-	0	-	0	-	1 (4.3)

	Olezarsen 80 mg (N = 22)		Olezarsen 50 mg (N = 21)		Placebo (N = 23)	
Nervous system disorders						
Headache	1 (4.5)	N/A	4 (19.0)	N/A	3 (13.0)	N/A
Psychiatric disorders						
Anxiety	0	N/A	3 (14.3)	N/A	0	N/A

Note: A TEAE was defined as any AE starting or getting worse on or after the first dose of the study drug. Note: For the summarization of number of patients (n), a patient was counted only once for each system organ class and preferred term even if he/she reported one or more events. Note: AEs were classified according to MedDRA Version 26.0. Abbreviations: AE = adverse event; COVID-19 = coronavirus infection 2019; MedDRA = Medical Dictionary for Regulatory Activities; N/A = not available; SAE = serious adverse event; TEAE = treatment-emergent adverse event. [1]All adverse events with a frequency of ≥ 10%; the hyphen (-) indicates that the AE is not reported in the data source, or that is reported but with a lower frequency than 10%. The ”0” is used when the AE is reported as 0 in the original source. [2]SAEs with a frequency of ≥ 3% in at least one treatment arm. Source: Stroes et al. 2024 [1].

9. Extrapolation of patient transitions

9.1 Clinical Data Used for Extrapolation of Patient Transitions

As stated in Section 4, the model health states are based on TG level and history of AP. AP and CP are clinically relevant outcomes in patients with FCS. The risk of AP and CP increases with TG levels, and Tryngolza® lowers TG levels [1, 6]. Tryngolza® also has an indirect treatment effect on mortality as studies have shown that AP and CP are associated with an increased risk of death, as presented in 3.1.1 [4, 11].

In the Balance trial, patients were followed for approximately one year. To estimate long-term complications, such as CP and death, external data was used, which is summarised in Table 19. To capture change in risk over time, the model incorporates 5 transition matrices; for 0-3 months, 3-6 months, 6-12 months, 1-2 years, and 2+. After two years, patients remain in their health state for the remaining part of the time horizon.

Table 19 Data sources for transition probabilities

Health state	Reference	Comment

Change in TG level (all TG and AP/history health state)	Balance [1]	
Risk of AP in the AP naïve and 1 AP health states	CALIBER [6]	No AP events were observed in the Balance trial for patients that were AP naïve or had had 1 AP, therefore external data was used
Risk of AP in the recurrent AP health states	Balance baseline data [1]	The model uses baseline data on the number of APs experienced by the trial subjects over the last 10 years before entering the trial
Risk of CP	Yadav et al [10]	Chronic pancreatitis was not measured in the Balance trial but is a key clinical outcome for patients with FCS
Death	Javed et al. [34] and Nøjgaard et al [11].	Background mortality from the Danish general population is applied to all health states. Increased risk of mortality for patients in the CP health state was sourced from Nøjgaard et al. The risk of instantaneous death from an AP event is estimated from Javed et al and was validated by a Danish clinical expert[39].

9.2 Extrapolation Using Parametric Extrapolation Models – N/A

9.2.1 Extrapolation of [Clinical Outcomes 1] N/A

Table 20. Overview of assumptions related to extrapolation of [clinical outcome] N/A

Method/approach	Description/assumption
Data	[Study name, source]
Selected distribution	[Intervention: X distribution] [Comparator: X distribution]
Models examined	[Describe which parametric extrapolation models were examined]
Assumptions	
Proportional hazards between intervention and comparator	[Yes/No] If 'Yes': Briefly describe modelling (joint vs. separate)
Flexible parametric models	[Yes/No] If 'Yes': Briefly describe the model
Cure point and/or share	[Yes/No] If 'Yes': Briefly describe the assumption/method
Treatment waning	[Yes/No] If 'Yes': Briefly describe the assumption/method
Other assumptions	[Yes/No] If 'Yes': Briefly describe the assumption/method
Internal validity	
Distribution with best AIC fit	[Intervention: X distribution] [Comparator: X distribution]
Distribution with best BIC fit	[Intervention: X distribution] [Comparator: X distribution]
Distribution(s) with best visual fit on probability scale (e.g., Kaplan-Meier data)	[Intervention: X distribution] [Comparator: X distribution]
Distribution(s) with best visual fit according to evaluation of smoothed hazards	[Intervention: X distribution] [Comparator: X distribution]

Method/approach	Description/assumption
External validity	
Sources for validating external validity	[Specify sources]
Distribution with highest external validity	[Intervention: X distribution] [Comparator: X distribution]

9.2.2 Extrapolation of [Clinical Outcome 2]

9.3 Extrapolation Using Transition Probabilities

The table "Transition probabilities in the health economic model" have been duplicated and presented separately for transition between TG and AP categories. The table for the transition between TG categories is presented in E.2.

Table 21 summarises the calculations used to derive the transitions between AP health states. $p_{(i,e)\rightarrow(j,f),t\rightarrow t+1}$ is the probability of transitioning from health state (i,e) (where i=TG category, e=AP category) at time t (beginning of the cycle) to health state (j,f) at time t+1 (end of the cycle). $AP_prob_{i,e}$ is probability of experiencing an AP in a given health state, $CP_prob_{i,e}$ the probability of developing CP in a given health state, and AP_m is the probability of an AP event being fatal.

Calculations are the same across treatment arm and time period.

Table 21. Transition probabilities in the health economic model

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
AP naïve	AP naïve	[redacted]	[redacted] calculates the TG transition probabilities based on IDP data.	TG transition probabilities: see Table 23 TG levels: Balance [1] AP risk: See page 68 CP risk: See page 70 AP mortality risk: see page 71
1AP	1AP			

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
AP naïve	1AP	[redacted]	Same as above	Same as above
1AP	AP recurrent			
Recurrent	Recurrent	[redacted]	Same as above	Same as above
Any health state	CP	[redacted]		Same as above
Any health state	Dead AP	[redacted]		Same as above

Table 22. Transition matrix [intervention/comparator]

Off/On	State A	State B	State C	…
N/A				
…				

Triglyceride levels

The model uses individual patient data (IPD) from the Balance trial to inform the transition between TG health states. The use of IPD permits the application of the stopping rules (Figure 2) to individual patients before their allocation to the transition matrices. Each patient's TG level at each model timepoint is allocated one of four TG categories:

Category 0: TG <500 mg/dL *(corresponding to approximately TG <5.6 mmol/L)*

Category 1: TG ≥500 mg/dL and <880 mg/dL *(corresponding to approximately TG ≥5.6 and <10 mmol/L)*

Category 2: TG ≥880 mg/dL and <2,000 mg/dL *(corresponding to approximately TG ≥10 and <22.6 mmol/L)*

Category 3: TG ≥2,000 mg/dL *(corresponding to approximately TG ≥22.6 mmol/L)*

The occupied TG category at each timepoint is then used to generate transition matrices in the form TG category t->TG category t+1, where t is the model cycle period.

The use of IPD to estimate proportions of patients transitioning between the TG health states ensures that the model closely reflects observed clinical outcomes, without requiring additional assumptions. Time-dependent transition probabilities were implemented, allowing for transitions to vary over time in line with observed disease progression.

Table 23 Transition probabilities in the health economic model between TG health states

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
TGs<500 Olezarsen (0-3 months)	TGs<500	[redacted] $p_{ij,t\to t+1} = \frac{n_{ij,t\to+1}}{n_{i,t}}$ n_{ij} = the number of patients transitioning from TG state i to j n_i = the number of patients initially in TG category i at the beginning of the cycle The same calculation is used for all following transition probabilities.	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
TGs 500<880 Olezarsen (0-3 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs 880<2,000 Olezarsen (0-3 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs≥2,000 Olezarsen (0-3 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
TGs<500 Olezarsen (3-6 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs 500<880 Olezarsen (3-6 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs 880<2000 Olezarsen (3-6 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
TGs≥2,000 Olezarsen (3-6 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs<500 Olezarsen (6-12 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs 500<880 Olezarsen (6-12 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
TGs 880<2000 Olezarsen (6-12 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs≥2,000 Olezarsen (6-12 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs<500 Olezarsen (1-2 years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
TGs 500<880 Olezarsen (1-2 years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs 880<2000 Olezarsen (1-2 years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs≥2,000 Olezarsen (1-2 years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
TGs<500 Olezarsen (2+ years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs 500<880 Olezarsen (2+ years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs 880<2000 Olezarsen (2+ years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
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	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
TGs≥2,000 Olezarsen (2+ years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs<500 SoC (0-3 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
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	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs≥2,000 SoC (3-6 months)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
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	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
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	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs<500 SoC (1-2 years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs 500<880 SoC (1-2 years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
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From health state	To health state	Transition probability, incl. calculation	Assumption	Source
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	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs≥2,000 SoC (1-2 years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs<500 SoC (2+ years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]

From health state	To health state	Transition probability, incl. calculation	Assumption	Source
TGs 500<880 SoC (2+ years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs 880<2000 SoC (2+ years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
TGs≥2,000 SoC (2+ years)	TGs<500	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 500<880	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs 880<2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]
	TGs≥2,000	[redacted]	Based on IPD data from Balance	Balance [56, 57]

Abbreviations: TGs, Triglycerides; SoC, Standard of Care

Acute pancreatitis

The modelled risk of AP depends on the health state occupied in the model, with an increasing risk of AP with TG levels and a history of AP [3-5, 17, 23-26]. Risk in the recurrent AP health states was estimated using the medical history AP rate from the Balance study. The number of AP events in the past 10 years from Balance was used to calculate a rate per patient-year, stratified by the patient's baseline TG category. Due to a small number of recurrent patients in the lowest two TG categories in Balance, they were combined into a single <880 mg/dL category.

There were no observed AP events among patients who were AP naïve or had experienced only one AP event during the trial period [58]. However, these patients are expected to experience AP over a lifetime horizon. The risk of AP for the AP-naïve and 1 AP health states was therefore estimated from the UK observational study CALIBER. CALIBER analysed linked primary and secondary care records from 1997 to 2016 for 15 million people in the UK to investigate how TG levels relate to the risk of comorbidities and clinical events, including AP, CP, and mortality. Patients of all ages were eligible for inclusion if they had at least one TG measurement recorded. A key limitation was that the CALIBER study was conducted in sHTG patients, not FCS patients, potentially underestimating AP rates even after adjusting for TG levels. This because the risk of experiencing an AP is higher in FCS patients than in patients with sHTG, as stated in section 3.1.1.2 [31].

Exponential regression models were fitted to patient data from CALIBER, which allocated risk of AP to the model health states. AP rates for the two lowest TG categories (<500 mg/dL category and <880 mg/dL category) were assumed to be the same, as the <500 mg/dL category did not exist in the CALIBER regressions. A limitation of the exponential models is that they do not capture the time-varying risks. To derive the treatment effect observed in Balance, calibration factors are used to adjust the rate ratio between the treatment arms [59, 60]. For details please see Appendix E.2.1.

The per cycle probability for AP is presented in Table 24.

Table 24 AP risk

	Tryngolza®	SoC
	Cycle probability	
TGs<500 AP naïve	[redacted]	[redacted]
TGs 500<880 AP naïve	[redacted]	[redacted]
TGs 880<2,000 AP naïve	[redacted]	[redacted]
TGs≥2,000 AP naïve	[redacted]	[redacted]

TGs<500 1 AP	[redacted]	[redacted]
TGs 500<880 1 AP	[redacted]	[redacted]
TGs 880<2,000 1 AP	[redacted]	[redacted]
TGs≥2,000 1 AP	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]
TGs≥2,000 Rec AP	[redacted]	[redacted]

Diabetes

A regression model was also used to predict the incidence of diabetes over the model time horizon. The probability of developing diabetes is estimated using exponential models from the CALIBER study [59, 60].

The probability of developing diabetes was conditionally applied to the patients without diabetes at baseline, presented in Table 25 As no data was available regarding the risk of diabetes for patients in the recurrent health states, the risk was assumed to be the same as for patients in the 1 AP health states. To ensure clinically relevant estimates, the prevalence of diabetes is capped at levels reported in relevant literature (see Table 67 for more information) The treatment effect of Tryngolza® on diabetes is derived from the movement of patients to better TG/AP health states while on treatment.

Table 25 Event rates - Annual probability of diabetes

Health state		CALIBER
AP Naïve	TGs < 500	1.3%
	TGs 500 < 880	1.3%
	TGs 880 < 2,000	11.9%
	TGs ≥ 2,000	13.0%
1 AP	TGs < 500	4.9%
	TGs 500 < 880	4.9%
	TGs 880 < 2,000	17.5%
	TGs ≥ 2,000	48.0%

Recurrent AP	TGs < 500	4.9%
	TGs 500 < 880	4.9%
	TGs 880 < 2,000	17.5%
	TGs ≥ 2,000	48.0%

Abbreviations: AP, Acute pancreatitis; FCS, Familial chylomicronemia syndrome; TG, Triglyceride

Chronic pancreatitis

The probability of developing CP in the model was derived from Yadav et al. (2012), which is a large, longitudinal study providing robust real-world estimates of progression to CP from the first AP event among 7,456 Pennsylvania residents who received a first-time AP diagnosis from 1996 through 2005 [10]. This is calculated as the product of the probability of an AP event in a given health state and the probability of developing CP following the AP event. The prevalence of CP in the study was 2.5% after 100 months among patients who had previously experienced one AP (n=6,010). For patients who had experienced recurrent AP events (n = 1,752), the CP prevalence was 12.5% after 100 months. Adjusting for time, the resulting annual probabilities of developing CP for a single and recurrent AP event are 0.3% and 1.6%, respectively. The long-term peak prevalence of CP was capped at 40% to ensure clinical plausibility, in line with the NICE evaluation of volanesorsen for FCS [61]. This was done by multiplying the CP rates for the 1 AP and recurrent AP health states with a factor of 1.8 [52]. The annual probabilities of CP are presented in Table 26.

The Yadav study was selected over the CALIBER study, which can also be used estimate the risk of CP, as CALIBER produced clinically unrealistic CP prevalence (>70%). The CALIBER estimate is included as a scenario analysis, where probabilities are obtained using a similar methodology to the AP regression models with CALIBER. As the CALIBER study did not provide results stratified by one vs recurrent AP, for the recurrent AP states, the probabilities from CALIBER were adjusted by the CP rate ratio for recurrent vs 1 AP from Yadav (1.6% for recurrent AP vs 0.3% for 1 AP) .

Table 26 Event rates - Annual probability of CP

Health state		Yadav et al. [52]
AP naïve	TGs < 500	0.30%
	TGs 500 < 880	0.30%
	TGs 880 < 2,000	0.30%
	TGs ≥ 2,000	0.30%
1 AP	TGs < 500	2.82%

	TGs 500 < 880	2.82%
	TGs 880 < 2,000	2.82%
	TGs ≥ 2,000	2.82%
Recurrent AP	TGs < 500	2.82%
	TGs 500 < 880	2.82%
	TGs 880 < 2,000	2.82%
	TGs ≥ 2,000	2.82%

Abbreviations: AP, acute pancreatitis; CP, chronic pancreatitis; FCS, familial chylomicronemia syndrome; TG, triglyceride

Mortality

The risk of an AP event being fatal was sourced from the assessment report of Waylivra for the treatment of FCS from the Swedish Dental and Pharmaceutical Benefits Agency (TLV). The mortality in AP among patients with FCS was estimated to be around 6% according to the company , which was confirmed by TLV's clinical expert. Additionally, TLV's clinical expert stated that approximately 10–20% of patients with APs develop a life-threatening condition, with mortality rates of up to 30% [62]. Based on this, a weighted average probability of death following an AP was estimated at 9.6%[1]. The TLV expert statement is supported by a study by Jadev et al, where it is stated that mortality of an AP event can approach 30% for those who develop pancreatic necrosis, infected abscesses, or multiple organ system failure [34].

CP is assumed to incur an excess risk of mortality relative to the general population mortality; the risk of mortality is applied to the entire health state.

Background mortality rate is estimated from the mortality of the age- and gender-specific Danish general population as per guidelines.

A summary of mortality-related inputs can be found in Table 27.

Table 27 Annual rates for probability of mortality

Mortality	Mean	Source
Probability AP is fatal	9.6%	Calculated from Jadev et al 2025 and TLV assessment report of Waylivra [34]

[1] $0.15 * 0.30 + 0.85 * 0.06 = 0.096 = 9.6\%$

Average SMR of CP	5.83	Nøjgaard et al., 2011. [11, 62].
General population mortality by age and sex	N/A	DMC guidelines

Abbreviations: AP, Acute pancreatitis; FCS, Familial chylomicronemia syndrome; RR, Relative rate; SMR, standardised mortality ratio

9.4 Summary and Validity of Extrapolated Patient Transitions

Table 28 presents the modelled LYs for both treatment arms over the model health states. Figure 7, Figure 8, Figure 9 and Figure 10 presents the health state occupancy over the time horizon.

The table and figures indicate that the extrapolated patient transitions are overall logical and clinically plausible across health states, treatment arms, and over time. During the observation period, the model reflects the expected progression of a chronic disease, with patients facing an increasing risk of transition from TG to AP and CP, as well as to death, as time progresses. The relative patterns between treatment arms also appear directionally consistent with the clinical expectations shown in the observed data.

Table 28. Modelled means in years, undiscounted estimates, half-cycle corrected and adjusted for background mortality

	Tryngolza® + SoC	No addition to SoC	Difference
Total life years	[redacted]	[redacted]	[redacted]
Life years in TGs<500 AP naïve	[redacted]	[redacted]	[redacted]
Life years in TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]
Life years in TGs 880<2000 AP naïve	[redacted]	[redacted]	[redacted]
Life years in TGs ≥2000 AP naïve	[redacted]	[redacted]	[redacted]
Life years in TGs<500 1 AP	[redacted]	[redacted]	[redacted]
Life years in TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]
Life years in TGs 880<2000 1 AP	[redacted]	[redacted]	[redacted]
Life years in TGs ≥2000 1 AP	[redacted]	[redacted]	[redacted]

	Tryngolza® + SoC	No addition to SoC	Difference
Life years in TGs<500 AP recurrent	[redacted]	[redacted]	[redacted]
Life years in TGs 500<880 AP recurrent	[redacted]	[redacted]	[redacted]
Life years in TGs 880<2000 AP recurrent	[redacted]	[redacted]	[redacted]
Life years in TGs ≥2000 AP recurrent	[redacted]	[redacted]	[redacted]
Life years in CP	[redacted]	[redacted]	[redacted]
Time on treatment Tryngolza® + SoC	6.34	0.00	6.34
Time on treatment No addition to SoC	15.42	18.35	-2.93

Abbreviations: SoC, Standard of Care; TGs, Triglycerides; AP, Acute pancreatitis; CP, Chronic pancreatitis

Figure 7. TG level health state occupation - Olezarsen



Figure 8. TG level health state occupation - SoC



Figure 9. AP health state occupation - Olezarsen



Figure 10. AP health state occupation - SoC



10. Health-Related Quality of Life

10.1 Overview

Table 29. Overview of included instruments for measuring health-related quality of life

Instrument	Median follow-up time and data-cut	Use	Source	Reference to description
Patient Global Impressions of Change (PGIC)	Median follow-up time is not available since PGIC is not a time-to-event endpoint. Data cutoff: 14 July 2023	Effect	Balance [1, 9]	10.2.1
Patient-Reported Outcomes Measurement Information System (PROMIS) 29+2 Profile	Median follow-up time is not available since PROMIS is not a time-to-event endpoint. Data cutoff: 14 July 2023	Effect, utility values	Balance [1, 9]	10.2.2

Table 30. Basis for estimating utility values

Instrument	Preference weights	Source	Short description
Utilities estimated from a vignette study	Vignette study with UK and Canadian participants	Matza et al [63]	The utilities estimated from Balance were associated with large uncertainties. Therefore, utilities from a vignette study inform the HSUVs for the base case

10.2 Instruments

10.2.1 Patient Global Impressions of Change (PGIC)

10.2.1.1 Study design and Instrument PGIC

PGIC is a patient-reported outcome measure that aims to capture how much a patient feels their condition has improved or worsened over time and was an exploratory analysis of the Balance trial. The PGIC score (scaled Much better = 1, A little better= 2, No change = 3, A little worse = 4, and Much worse =5) was tabulated by severity or change category and by treatment group over time, into two categories "improved" vs. "not improved" [9]. Improved was defined as change from baseline <0 and not improved was defined as change from baseline ≥0.

10.2.1.2 Data Collection PGIC

Table 31. Overview of responses olezarsen

Time	Number of patients "at risk "* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients "at risk " at time point *t*** %	Proportion of responses among patients at randomisation*** %
Month 6	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]	Olezarsen 50 mg: 19 Olezarsen 80 mg: 19	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: 86%	Olezarsen 50 mg: 90% Olezarsen 80 mg: 86%
Month 12	Olezarsen 50 mg: [redacted]	Olezarsen 50 mg: [redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]

Time	Number of patients “at risk ”* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients “at risk ” at time point *t*** %	Proportion of responses among patients at randomisation*** %
	Olezarsen 80 mg: [redacted]	Olezarsen 80 mg: [redacted]		

* Number of patients “at risk”: Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

Table 32 Overview of responses placebo

Time	Number of patients “at risk ”* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients “at risk ” at time point *t*** %	Proportion of responses among patients at randomisation*** %
Month 6	[redacted]	22	96%	96%
Month 12	[redacted]	[redacted]	[redacted]	[redacted]

* Number of patients “at risk”: Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

N/A, Table 33 could not be populated because the patient-level data is not available.

Table 33 Overview of responses by health states [create a table for both intervention and comparator]

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
Health state 1	500	99
Health state 2	100	60

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
Etc.	...	...

10.2.1.3 Results PGIC

PGIC does not generate a continuous score suitable for calculation of mean change from baseline and corresponding 95% confidence intervals. As PGIC captures patients' global impression of change using ordered response categories, the outcome is instead summarised as the percentage of patients classified as improved and not improved in the intervention and comparator groups at each follow-up.

[redacted]

Figure 11. PGIC at Months 6 and 12



Note: a, PGIC estimates patient's perception of an improvement ('much better' or 'a little better') in their condition following treatment. [b]p-values compared with placebo. [c]N numbers are based on the number of available patients at Month 6 and 12, respectively

Table 34 Results for PGIC olezarsen 50 mg

	Intervention		Comparator		Difference	
	Improved* n (%)	Not Improved** n (%)	Improved* n (%)	Not Improved** n (%)	Improved*n (SE)	Not Improved** n (SE)

	Intervention		Comparator		Difference	
Month 6	10 (52.6)	9 (47.4)	9 (40.9)	13 (59.1)	1 (N/A)	-4 (N/A)
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: *(PGIC score = Much better[< 1.5], A little better [1.5 to < 2.5]) **(PGIC score = No change [2.5 to < 3.5], A little worse [3.5 to < 4.5], Much worse [≥ 4.5]),

Table 35. Results for PGIC olezarsen 80 mg

	Intervention		Comparator		Difference	
	Improved* n (%)	Not Improved** n (%)	Improved* n (%)	Not Improved** n (%)	Improved*n (SE)	Not Improved** n (SE)
Month 6	15 (78.9)	4 (21.1)	9 (40.9)	13 (59.1)	6 (N/A)	-9 (N/A)
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note. *(PGIC score = Much better[< 1.5], A little better [1.5 to < 2.5]) **(PGIC score = No change [2.5 to < 3.5], A little worse [3.5 to < 4.5], Much worse [≥ 4.5]),

10.2.2 Patient-Reported Outcomes Measurement Information System (PROMIS) 29+2 Profile

10.2.2.1 Study Design and Instrument PROMIS 29 +2

In the Balance study, the Patient-Reported Outcome Measurement Information System (PROMIS) instrument was included. The PROMIS-29+2, a fixed-form profile HRQoL measure adapted from a reduced set of PROMIS items (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, cognition, and ability to participate in social roles and activities), and was anticipated to capture broader aspects of HRQoL [64, 65] in patients with FCS. The PROMIS-Preference measure (PROPr; a health utility measure) can be derived from the PROMIS-29+2 instrument, generating utilities directly, and the PROPr can in turn be mapped to EQ-5D utility values.

10.2.2.2 Data collection PROMIS 29 +2

Table 36. Overview of responses olezarsen

Time	Number of patients "at risk "* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients "at risk " at time point *t*** %	Proportion of responses among patients at randomisation*** %
Baseline	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]
Month 6	Olezarsen 50 mg:[redacted] Olezarsen 80 mg:[redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]
Month 12	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]	Olezarsen 50 mg: [redacted] Olezarsen 80 mg: [redacted]

* Number of patients "at risk": Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

Table 37 Overview of responses placebo

Time	Number of patients "at risk "* at time point *t* (expected number of responses) N	Number of responses at time point *t* N	Proportion of responses among patients "at risk " at time point *t*** %	Proportion of responses among patients at randomisation*** %
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]

* Number of patients "at risk": Patients who have not died or been censored before time point *t*, and are therefore expected to complete the questionnaire. Patients who discontinued treatment must be included.

**Proportion of responses among patients "at risk" at time point *t* = number of responses at time *t* / number of patients "at risk" at time *t*.

***Proportion of responses since randomisation = number of responses at time *t* / number of patients at randomisation.

Table 38 presents the overview for responses, i.e., sample size, for PROMIS 29+2 that that form the basis for the mapping.

Table 38. Overview of responses by health states [create a table for both intervention and comparator]

Health state	Number of responses in the health state N	Number of patients who provided at least one response in the health state N
AP naïve TGs<880	[redacted]	N/A, patient level data not available
AP naïve TGs 880<2000	[redacted]	N/A, patient level data not available
AP naïve TGs≥2,000	[redacted]	N/A, patient level data not available
1 AP TGs<880	[redacted]	N/A, patient level data not available
1 AP TGs 880<2000	[redacted]	N/A, patient level data not available
1 AP TGs≥2,000	[redacted]	N/A, patient level data not available
Recurrent AP TGs<880	[redacted]	N/A, patient level data not available
Recurrent AP TGs 880<2000	[redacted]	N/A, patient level data not available
Recurrent AP TGs≥2,000	[redacted]	N/A, patient level data not available

10.2.2.3 Results PROMIS 29+2

This section presents results for the PROMIS Preference score (PROPr), a health utility measure derived from PROMIS domain scores. [redacted]. The result from PROMIS 29+2 was mapped to EQ-5D-5L DK as presented in Appendix G. This was associated with large uncertainties (see Appendix G), whereas utilities from a vignette study is used in the base case.

Figure 12. Change from baseline PROPr



Table 39. Results for PROMIS 29 +2 (PROPr) olezarsen 50 mg

	Intervention	Comparator	Difference
	Mean (SE)	Mean (SE)	Difference (95% CI)
Baseline	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]

Table 40 Results for PROMIS 29 +2 (PROPr) olezarsen 80 mg

	Intervention	Comparator	Difference
	Mean (SE)	Mean (SE)	Difference (95% CI)
Baseline	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]

10.2.3 Summary when reporting multiple instruments

Both PGIC and PROMIS was measured in the Balance trial. PGIC provides a direct and clinically intuitive measure of perceived overall change, whereas PROMIS offers a

broader and more detailed assessment of HRQoL and was used to derive utility values which is further described in section 10.3.

10.3 Utility Values

10.3.1 Data Sources

As presented in section 10.2.2, HRQoL was measured through PROMIS in the Balance trial. Danish EQ-5D-5L health state utilities were estimated from the PROMIS utilities through two mapping algorithms (see 10.3.4). HRQoL associated with AP and CP events was not measured in Balance and therefore disutilities for these events were estimated from literature.

The Health state utility values (HSUVs) for the TG/AP history health states, mapped from the Balance trial, were associated with large uncertainties, as presented in 10.3.4. Measuring HRQoL and estimating utilities in rare diseases is challenging because studies often include small, heterogeneous patient populations [66, 67]. Vignette-based utilities are therefore a useful approach in rare diseases, as they can be tailored to relevant health issues while reducing reliance on scarce patient-level data [68]. In the base case, HSUVs from a vignette study were used.

All HSUVs were age-adjusted in accordance with the DMC methodological guidelines.

10.3.2 Adverse Events, Comorbidity and Other State-Specific Adjustments to Utility Values

As mentioned above, HRQoL for patients with CP was not measured in Balance and therefore sourced from literature. In the base case, the CP HSUV was assumed based on Matza, et al [63]. CP was assumed to take the worst vignette chronic health state value (TG ≥2,000 mg/dL and recurrent AP) with monthly decrements of AP representing painful CP "flares". This ensured that the CP health state, which is an absorbing health state, had lower utility that the most severe TG/AP health state.

Disutilities associated with AP, CP, and diabetes are presented in Table 41.

Table 41. Utility decrements

Description	Disutility	Source	Duration (days)	Source
AP (base case, from vignettes)	0.23	Matza et al., 2020 [51]	9.6	Duration calculated from APPROACH data. In the IN-FOCUS survey (Davidson et al., 2018), approximately 50% of patients reported that they visited the hospital for every AP

				episode. Duration is doubled to account for this.[69]
Disutility Diabetes (uncomplicated)	0.04	Diabetes Mellitus ICD 250, Sullivan et al., 2009[70]	Chronic	Chronic health state. Applied to AP naïve health states.
Disutility with number of chronic conditions (NCC) x2	0.094	Disutility for 2 Chronic conditions (NCC) US, Sullivan et al., 2009 [70]	Chronic	Chronic health state.
Disutility of diabetes applied to recurrent AP states	0.13	Sum of the disutility of uncomplicated diabetes + the disutility of 2x NCC	Chronic	Chronic health state. Applied to recurrent AP health states.
Disutility of diabetes applied to 1 AP states	0.08	Mid-point of the disutility of uncomplicated diabetes and the disutility of complicated diabetes (2x NCC)	Chronic	Chronic health state. Applied to 1 AP health states.
Annual disutility from CP abdominal pain flares	0.07	Assumed monthly AP 'flares'	Chronic	Matza et al [63]

10.3.3 Results for Utility Values

Table 42. Utility values used in the health economic model

	Utility value [95% CI]	Instrument, preference weight	Source and reference
Main analysis			
AP naïve TGs<500	0.80	Vignette	Matza et al, Table 2 [63]
AP naïve TGs 500<880	0.80	Vignette	Matza et al, Table 2 [63]
AP naïve TGs 880<2,000	0.70	Vignette	Matza et al, Table 2 [63]

	Utility value [95% CI]	Instrument, preference weight	Source and reference
AP naïve TGs≥2,000	0.60	Vignette	Matza et al, Table 2 [63]
1 AP TGs<500	0.77	Vignette	Matza et al, Table 2 [63]
1 AP TGs 500<880	0.77	Vignette	Matza et al, Table 2 [63]
1 AP TGs 880<2,000	0.65	Vignette	Matza et al, Table 2 [63]
1 AP TGs≥2,000	0.53	Vignette	Matza et al, Table 2 [63]
Recurrent AP TGs<500	0.74	Vignette	Matza et al, Table 2 [63]
Recurrent AP TGs 500<880	0.74	Vignette	Matza et al, Table 2 [63]
Recurrent AP TGs 880<2,000	0.60	Vignette	Matza et al, Table 2 [63]
Recurrent AP TGs≥2,000	0.46	Vignette	Matza et al, Table 2 [63]
Scenario analysis			
AP naïve TGs<500	XXXX	EQ-5D-5L, DK	Balance CSR chapter 9.5, Tang et al, and Torkilseng et al [9, 71, 72]
AP naïve TGs 500<880	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500
AP naïve TGs 880<2,000	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500
AP naïve TGs≥2,000	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500
1 AP TGs<500	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500
1 AP TGs 500<880	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500

	Utility value [95% CI]	Instrument, preference weight	Source and reference
1 AP TGs 880<2,000	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500
1 AP TGs≥2,000	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500
Recurrent AP TGs<500	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500
Recurrent AP TGs 500<880	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500
Recurrent AP TGs 880<2,000	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500
Recurrent AP TGs≥2,000	XXXX	EQ-5D-5L, DK	Same as AP naïve TGs<500

[a] Actual converted value was 1.04, which was capped to 1.00

10.3.4 Calculation of Utility Values

The PROMIS-Preference measure (PROPr; a health utility measure) can be directly derived from the PROMIS-29+2 instrument. The PROPr can in turn be mapped to EQ-5D-3L index scores using a recently published mapping algorithm [71]. Further, the EQ-5D-3L with UK tariffs were mapped to EQ-5D-5L with Danish tariffs using a mapping algorithm proposed by Torkilseng et al [72]. Details on the mapping to EQ-5D-5L DK are presented in Appendix G.3 and the result in Table 42.

After mapping from PROMIS-21+2 to EQ-5D-3L UK, multiple regression models were examined to derive the TG/AP history health states.

Several ordinary least squares (OLS) models were explored. Treatment arm (olezarsen vs placebo) was a significant predictor of HRQoL in the models that included only baseline EQ-5D-3L and treatment arm. These models predicted that treatment with olezarsen had a negative relationship with HRQoL, compared to treatment with placebo. The most clinically realistic results were generated by OLS models with 3-level categorical predictor variables for TG levels and AP events. With these models, a worsening of utility with higher TG levels and/or number of historical AP events was observed. OLS models with interaction terms between TG and AP categories were also explored, however statistical significance was reduced, and these models predicted utility values that were not aligned with the observed data. Regression estimates of the greatest magnitude for effect of TG were obtained when only baseline results were included in the analysis. An increase in TG levels and AP events was linked to an important decline in utility. However, statistical significance was limited in this analysis, especially for TG prediction categories.

After several model iterations, OLS 19 was found to be the best fitting model. Statistical details on the choice of regression model, the exact specification of regression equations, and the resulting outputs are presented in G.4. As OLS 19 also generated the most clinically realistic results, this analysis was selected to inform the FCS utilities generated using trial results.

However, the OLS models have several limitations. These limitations include very small patient numbers in the low TG health states at baseline, leading to utility values at least similar to or higher than the population norms in the least severe health states. This lacks face validity since restricted diet alone would be expected to lead to lower utility than the general population. Furthermore, the small sample size and number of model health states precluded the use of repeated measures models, which are the preferred method of generating utility values when there are multiple assessment timepoints per patient. Initial attempts at generating utility values using repeated measures models predicted increasing utility with increasing TG level, which lacks face validity.

Therefore, a set of utility values were derived from a vignette study by Matza et al. [63]. The estimated utilities from the study of Matza et al have been previously submitted to NICE in an assessment of an FCS intervention [73]. The vignette study valued four FCS chronic health state descriptions. The health states are AP naïve with low TGs, AP naïve with high TGs, history of AP with low TGs, and history of AP with high TGs. The AP naïve vignette values were applied to the AP naïve model health states, the AP-experienced vignette values were applied to the recurrent AP health states, and the average of the two vignettes were applied to the 1 AP health states, with the assumption that 50% of 1 AP patients have lingering symptoms of their AP. CP was assumed to take the worst vignette chronic health state value (TG ≥2,000 mg/dL and recurrent AP) with additional decrements of AP representing painful CP flares.

In the vignette study, TG health states were not specifically defined numerically. Therefore, for the TG levels, a 'sliding scale' approach has been used to apply the two vignettes (low and high) to the four TG categories used in the model. The two lowest TG categories (TGs<500 and TGs 500<880) are assigned the utility value based on the 'low TG' vignette, the highest TG category (TGs≥2,000) is assigned the utility of the 'high TG' vignette, and an average of the two utilities is calculated and assigned for the TGs 880<2,000 category.

11. Calculations of Costs

11.1 Drug Costs

11.1.1 Drug Costs for Intervention and Comparator

In the model, Tryngolza® is administered as a subcutaneous injection once per month (12 doses per year) as per SmPC [38]. SoC includes a strictly fat reduced diet.

Dose pauses for Tryngolza® observed during the Balance study are captured in the model as a dose intensity. The dose intensity of Tryngolza® is assumed to be 96% [9].

According to the SmPC, some patients may not be responsive to treatment with Tryngolza® after 6 months, in such a case the discontinuation of Tryngolza® should be considered on an individual basis by the prescribing physician [38]. In the model, a response assessment with a stopping rule is included as a decision tree. Patients who do not achieve the selected response level are assumed to discontinue active treatment and transition to SoC alone for the reminder of the model time horizon. Since there are no defined response criteria in the SmPC, the response assessment for Waylivra® (volanesorsen) is included in the base case, which requires a reduction in TGs of ≥25% or absolute TGs <2,000 mg/dL (22.6 mmol/L) to continue treatment after 3 months [74]. However, for Tryngolza®, this occurs at month 6 in the model. To avoid overestimates of discontinuation, the proportion discontinuing from each TG health state at the timepoint of the stopping rule is set to be the maximum of discontinuation from either the stopping rule or all-cause discontinuation, not the sum of both. Based on patient-level data from Balance, at month 6, 25% of the patients are expected to discontinue treatment of Tryngolza® due to not achieving the selected response levels.

In addition, an annual discontinuation rate of 9.09% is applied to Tryngolza® patients based on the two patients who discontinued treatment (80 mg dose) in the Balance study [75]. A third patient discontinued due to moving, but this is not considered relevant to clinical practice, as access would not be dependent on proximity to trial site. Hence, this patient is not included in calculation of Tryngolza®'s discontinuation rate. Due to lack of evidence on the long-term discontinuation of Tryngolza® the same discontinuation rate was assumed for the remaining model time horizon beyond the duration of the Balance study.

11.1.2 Drug Costs for Subsequent Treatment

Patients who discontinue treatment with Tryngolza® continue on SoC.

11.2 Hospital Costs

11.2.1 Administration

Table 43. Assumptions regarding administration costs

Route of administration	Diagnosis and procedure codes*	DRG group	Unit cost, DKK
Subcutaneous injection of Tryngolza®	N/A (self-administered)	N/A	0
Oral administration of SoC treatments	N/A (self-administered)	N/A	0

*Include other patient information if relevant for the choice of DRG group; A = action diagnosis

11.2.2 Disease Management

The resource use for disease management is informed CALIBER data [59] on the specified TG categories for all activates but outpatient visits that was sourced from a Danish clinical expert [39].

Table 44. Assumptions regarding disease management costs

Activity/pathway	Frequency (annual event rate)	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
Inpatient hospital	[redacted] XXX	>=12 timer	A (DE783A)	10MA04 Ernærings- og diverse metaboliske sygdomme	DKK 23,275
A&E visits	[redacted]	>=12 timer	A (DE783A)	10MA04 Ernærings- og diverse metaboliske sygdomme	DKK 23,275
GP visits	XXXXXXXXX [redacted]	< 12 timer (kort)	A (DE783A) P (ZZ0149AX)	10MA98 MDC10 1-dagsgruppe, pat. mindst 7 år	DKK 2,150
Outpatient visits	[redacted] [39]	< 12 timer (kort	A (DE783A) P (ZZ0149AX)	10MA98 MDC10 1-dagsgruppe, pat. mindst 7 år	DKK 2,150

*Include other patient information if relevant for the choice of DRG group; A = action diagnosis; P = procedure.

11.2.3 Treatment Monitoring

The frequency of a general practitioner visit and outpatient visits is based on NICE assessment report of Waylivra®.

Table 45. Assumptions regarding costs for treatment monitoring

Activity/Pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
Self-administration training session	Once	1 hour	A (DE783A) P (BZFC3)	10MA98 MDC10 1-dagsgruppe, pat. mindst 7 år	DKK 2,150

*Include other patient information if relevant for the choice of DRG group; A = action diagnosis; P = procedure.

11.2.4 Management of adverse events

No serious treatment emergent adverse events (TEAEs) related to study drug were observed in the Balance trial [1]. Only mild events were observed and thus these were not included in the model as per DMC guidelines [9].However, two patients (8.7%) in the placebo arm experienced related proteinuria that was deemed severe. The model has the option to include the cost of treating proteinuria as a scenario analysis, which is assumed equivalent to a visit with a physician. This cost in applied to the first cycle in the placebo arm.

Table 46. Assumptions regarding costs for the management of adverse events - Scenario

Adverse event	Proportion		Diagnosis codes*	DRG group	Unit cost
	Tryngolza® + SoC	No addition to SoC			
Proteinuria	0%	Applied as a one-off cost in the first cycle	A (DR809) and P (DE783A), duration < 12 hours (short)	11MA98 1-dagsgruppe, pat. mindst 7 år	DKK 1,588

*Include relevant procedure codes and other patient information if relevant for the choice of DRG group; A = action diagnosis; B = secondary diagnosis.

11.2.5 Other Hospital Costs

No other hospital costs were included in the analysis.

11.3 Patient Costs

Patients costs associated with treatment monitoring, for the activities presented in Table 47, was included in the analysis as per the DMC guidelines [76].

Table 47. Assumptions regarding patient time

Activity	Frequency of activity	Time spent on activity	Transport time	Note
Self-administration training session	Once	1 hour	1.5 hour	Transportation time according to guidelines.
General practitioner visit	As per Table 44	1 hour	1.5 hour	Transportation time according to guidelines.
Outpatient visit	As per Table 44	1 hour	1.5hour	Transportation time according to guidelines.

11.4 Other Costs

Daily administration of fibrates, statins, and fish oils were allowed in the Balance study [1]. In the model these are included as concomitant treatments for all patients as a conservative assumption.

Event costs associated with AP, CP and diabetes are presented in Table 48. In the model, diabetes and CP events are modelled to incur annual costs, which are assumed representative with costing through DRG.

Table 48. Event costs

Event	Health economic model	Diagnosis and procedure code	DRG code	Cost
Diabetes	Annual cost	A (DE119A) P (DE783A) >=12 timer	10MA03 Diabetes mellitus.	DKK 42,646
Chronic pancreatitis	Annual cost	A (DK850) B (DE783A >=12 timer	07MA11 Sygdomme i bugspytkirtel, ekskl. Ondartede sygdomme	DKK 39,913

Acute pancreatitis	One-off event cost	A (DK850) B (DE783A >=12 timer	07MA11 Sygdomme i bugspytkirtel, ekskl. Ondartede sygdomme	DKK 39,913

12. Results

The results of the base case show that the cost of an additional QALY gained from treatment with Tryngolza® compared to no addition to SoC is predicted to be DKK [redacted]. Treatment with Tryngolza® is predicted to lead to a gain of [redacted] additional quality-adjusted life years (QALYs) and [redacted] additional life years (LYs). It is predicted that treatment with Tryngolza® will lead to an additional cost [redacted] compared to treatment with SoC alone. The results of the base case analysis are presented in Table 49.

Table 49. Results, discounted estimates, half-cycle corrected (where relevant), and adjusted for background mortality

	Tryngolza®	No addition to SoC	Difference
Drug costs	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Disease management	[redacted]	[redacted]	[redacted]
Chronic pancreatitis	[redacted]	[redacted]	[redacted]
Acute pancreatitis	[redacted]	[redacted]	[redacted]
Diabetes	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
LYs in TGs<500 AP naïve	[redacted]	[redacted]	[redacted]
LYs in TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]
LYs in TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]
LYs in TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]

	Tryngolza®	No addition to SoC	Difference
LYs in TGs<500 1 AP	[redacted]	[redacted]	[redacted]
LYs in TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]
LYs in TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]
LYs in TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]
LYs in TGs<500 Rec AP	[redacted]	[redacted]	[redacted]
LYs in TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]
LYs in TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]
LYs in TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]
LYs in CP	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs in TGs<500 AP naïve	[redacted]	[redacted]	[redacted]
QALYs in TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]
QALYs in TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]
QALYs in TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]
QALYs in TGs<500 1 AP	[redacted]	[redacted]	[redacted]
QALYs in TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]
QALYs in TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]
QALYs in TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]
QALYs in TGs<500 Rec AP	[redacted]	[redacted]	[redacted]
QALYs in TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]

	Tryngolza®	No addition to SoC	Difference
QALYs in TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]
QALYs in TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]
LYs in Chronic pancreatitis	[redacted]	[redacted]	[redacted]
QALYs in AP	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained		[redacted]	
Incremental costs per QALY gained (ICER)		[redacted]	

Table 50. Results per drug in combination treatments N/A

	Drug costs
Intervention: Drug A	
Intervention: Drug B	
…	
Comparator: Drug C	
Comparator: Drug D	
...	

12.1 Sensitivity Analyses

12.1.1 Deterministic Sensitivity Analyses

The impact of individual parameters on the ICER were tested in scenario analyses, which are presented in Table 51.

Table 51. Results of deterministic sensitivity analyses

Deterministic sensitivity analysis	Incremental costs	Incremental QALYs	ICER
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: TG, Triglyceride; AP, Acute pancreatitis; Rec, Recurrent

12.1.2 Probabilistic Sensitivity Analyses (PSA)

Plots from the probabilistic sensitivity analysis, including a scatter plot, cost-effectiveness acceptability curve, and ICER convergence plot are presented in Figure 13, Figure 14, and Figure 15, respectively. The incremental cost-effectiveness scatterplot presents the variation in incremental costs and QALYs over 1,000 replications of Tryngolza® + SoC vs no addition to SoC. Based om the results of the 1,000 simulations, the mean ICER was DKK [redacted]. The majority of replicated outcomes fell within the northeast quadrant, indicating higher costs and better outcomes.

Figure 13. Scatter plot



Figure 14 presents the cost-effectiveness acceptability curve. At a WTP of DKK 8,000,000 the probability of Tryngolza as an add on to SoC to be cost-effectiveness is [redacted].

Figure 14. Tryngolza® CEAC



Figure 15 presents the ICER convergence plot. Around 100 iterations the ICER starts to converge around [redacted] DKK.

Figure 15. ICER convergence plot



13. Budget Impact Analysis

The budget impact analysis according to guidelines is presented in Table 52. However, we note that the excel template cannot accurately present the budget impact analysis according to our assumptions.

As presented in section 3.1.3, it is assumed that [redacted] patients are eligible for treatment with Tryngolza® in Denmark. The first year, it is assumed that [redacted] % (corresponding to [redacted] patients) will be treated. The following 3 years (2027, 2028 and 2029) [redacted] more patients will be treated, corresponding to a total of [redacted] patients receiving Tryngolza® in 2027, 2028 and 2029. Finally, in year 2030, all patients will be treated. In the DMC budget impact template, the market shares are calculated based on the incident population and not on the total prevalent patient population. Therefore, when assuming [redacted] patients eligible for treatment every year, the total number of patients in year [redacted] corresponds to [redacted] which exceeds the actual number of patients with FCS in Denmark. However, if we add [redacted] in the template, the template calculates the market share of [redacted] patients the following year, which will always correspond to [redacted].

Therefore, a simplified budget impact analysis is presented in Table 53. In the simplified budget impact, the annual cost of Tryngolza® is [redacted], which is based on a list price of [redacted] and assuming 12 doses per year.

Table 52. Budget impact (undiscounted estimates), mDKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Regional costs with recommendation					
Drug costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other regional hospital costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total with recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Regional costs without recommendation					
Drug costs	0.12	0.21	0.29	0.37	0.45
Other regional hospital costs	0.36	0.65	0.91	1.16	1.40
Total without recommendation	0.48	0.85	1.20	1.54	1.85
Total budget impact	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 53 Simplified budget impact analysis, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients eligible for treatment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patient share of Tryngolza®	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients treated with Tryngolza®	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sales estimate DKK (AIP)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of Experts

Dr. Nikolaj Thure Krarup, PhD, Ward Physician at the Lipid clinic, within cardiovascular research and heart rehabilitation at the Regional Hospital Viborg, Selikeborg and Skive, at the hospital department Midt, Region Midtjylland (cardiac diseases) [39].

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Appendix A. Study Characteristics

The main characteristics of the included study, Balance, are described in Table 54 below.

Table 54. Main characteristics of included studies

Study name: Balance	**NCT number: NCT04568434**
Objective	The Balance trial aimed to measure the efficacy and safety of olezarsen in addition to SoC compared with placebo in addition to SoC in patients with FCS.
Publications – title, author(s), journal, year	Olezarsen, Acute Pancreatitis, and Familial Chylomicronemia Syndrome. Erik S.G. Stroes, et al. The New England Journal of Medicine, 2024 [1].
Study type and design	A phase 3, randomised, multicentre, double-blind, placebo-controlled study. Patients underwent a screening period that was approximately 4 weeks, but no more than 8 weeks, which included an approximately 2-week diet/lifestyle stabilisation/run-in period for patients not yet on a stable diet (≤20 g fat/day), followed by an approximately 2-week qualification period. Following qualification, patients were randomly assigned 1:1. Randomisation was also stratified by prior history of pancreatitis within 10 years prior to screening and by previous treatment with volanesorsen. Episodes of AP were adjudicated by an independent committee in a blinded manner using the Atlanta classification of acute pancreatitis. Crossover was not part of the study design.
Number of trial participants (N)	*N = 66*
Primary inclusion criteria	• Written informed consent. • Enrolled patients were at least 18 years of age. • A diagnosis of familial chylomicronemia syndrome (type 1 hyperlipoproteinemia) by documentation of biallelic pathogenic variants (ie, homozygosity, compound heterozygosity or double heterozygosity) in FCS-causing genes (ie, *LPL, GPIHBP1, APOA5, APOC2,* or *LMF1*). • Fasting triglyceride levels ≥880 mg/dL (≥10 mmol/L) at screening. • History of pancreatitis within 10 years prior to screening. Patients without a recorded 10 history of pancreatitis, or no recorded history within 10 years prior to screening, were also eligible, but their enrolment was capped at 35% (ie, ≤21 of the 60 planned patients) • Willing to follow a diet comprising ≤20g of fat per day during the study. • Willing to complete all patient-reported outcome assessments throughout the study.

Study name: Balance	NCT number: NCT04568434
Primary exclusion criteria	• Clinically significant abnormalities in medical history (e.g., previous acute coronary syndrome within 6 months of screening, major surgery within 3 months of screening) or physical examination. • Active pancreatitis within 4 weeks prior to screening. • Screening laboratory results as follows, or any other clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion: a. Platelet count <100,000/mm3 at screening or qualification. If the platelet count was <100,000/mm3, up to 2 additional tests could be performed to qualify at both screening and qualification 12 b. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3.0 × upper limit of normal (ULN) c. Total bilirubin > ULN unless due to Gilbert's syndrome d. Estimated glomerular filtration rate <45 mL/min/1.73 m2 (as determined by the CKD-EPI formula for creatinine clearance) e. Urine protein to creatinine ratio (UPCR) ≥500 mg/g, or urine albumin to creatinine (UACR) ratio ≥300 mg/g • Uncontrolled arterial hypertension (blood pressure >160/100 mm Hg) • History of bleeding diathesis or coagulopathy or clinically significant abnormality in coagulation parameters at screening • Active infection requiring systemic antiviral or antimicrobial therapy that would not be completed prior to study day 1, or active COVID-19 infection with or without therapy that would not be resolved by study day 1 • Active infection with human immunodeficiency virus (HIV), hepatitis C, or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at screening who tested positive by serology but negative by RNA were allowed in consultation with the sponsor medical monitor • Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that had been successfully treated. Patients with a history of other malignancies that had been treated with curative intent and which had not recurred within 5 years were also eligible if approved by the sponsor medical monitor
Intervention	Patients received either 80 mg olezarsen (N = 22) or 50 mg olezarsen (N = 21) treatment by subcutaneous injection every 4 weeks for 49 weeks, in addition to standard of Care (SoC). Prior to treatment, patients underwent a 4-week screening period (total trial period was 53 weeks).

Study name: Balance	NCT number: NCT04568434
Comparator(s)	Patients received placebo (N = 22) for treatment by subcutaneous injection every 4 weeks for 49 weeks, in addition to SoC. Placebos were given as a matching volume to olezarsen, either 0.5 mL to match the 50 mg olezarsen group, or 0.8 mL to match the 80 mg olezarsen group. Prior to treatment, patients underwent a 4-week screening period (total trial period was 53 weeks).
Follow-up time	The **primary outcome** was the percentage change from baseline in fasting TG at 6 months of Tryngolza® compared to placebo; the follow-up time was 6 months. **For the secondary outcomes:** • Per cent change from baseline in fasting TG at Month 12 compared to placebo, the follow-up time was 12 months. • Episodes of AP at week 53, the follow-up time was 53 weeks. **Safety outcomes**: The recording of non-serious and serious adverse events (AEs) will begin after the patient signs the informed consent form and will end at the end of the patient's Follow-up Period (13 weeks post end of treatment). End of treatment is defined as 1 dosing interval post-last dose. **HRQoL outcomes:** • PROMIS 29+2, a fixed-form profile HRQoL, was used to assess patients' HRQoL and follow-up at months 6 and 12. • Exploratory assessment of the responses of the patient-reported outcome PGIC was followed up at month 6 and month 12.
Is the study used in the health economic model?	Yes
Primary, secondary, and exploratory outcomes	**Statistical method and information:** Descriptive summary statistics were used to summarise most data. To control the overall Type I error rate at 0.05 across primary and secondary efficacy endpoints, the two olezarsen groups were controlled to a pooled placebo group for analyses, using a gatekeeping procedure that allowed a hierarchical testing of endpoints grouped by priority within the primary endpoint family and the secondary endpoint family. For primary analyses, the per cent change from baseline to the primary analysis time point in fasting TG was compared between each olezarsen treatment group vs the pooled placebo using an analysis of covariance (ANCOVA) model. The 95% confidence interval (CI) of the treatment differences was calculated using the robust variance estimator based on the Bell and McCaffrey method. **Outcomes included in this submission:** **Primary:**

- The two primary efficacy endpoints in order of hierarchy were the difference in the percent change in the fasting TG from baseline to 6 months in the 80-mg olezarsen group as compared with the placebo group and in the 50-mg olezarsen group as compared with the placebo group.

Secondary (28 outcomes):

Twenty-eight secondary endpoints were prespecified and rank prioritised to be analysed in hierarchical order. If the comparison of the first secondary endpoint was statistically significant (P <0.05), then the second secondary endpoint was tested. However, if the comparison of the first secondary endpoint was not statistically significant, then all endpoints of lower rank were considered exploratory. This process was repeated with each subsequent secondary endpoint. The rank-prioritised secondary endpoints are listed below. Only the first two secondary outcomes were included in this application.

1. Comparison of per cent change in fasting triglycerides from baseline to month 12 between the olezarsen 80-mg treatment group and pooled placebo in the FAS

2. Comparison of per cent change in fasting apolipoprotein C-III from baseline to month 6 between the olezarsen 80-mg treatment group and pooled placebo in the FAS

3. Comparison of per cent change in fasting apolipoprotein C-III from baseline to month 12 between the olezarsen 80-mg treatment group and pooled placebo in the FAS

4. Comparison of proportion of patients who achieve ≥ 40% reduction in fasting triglycerides from baseline to month 6 between the olezarsen 80-mg treatment group and pooled placebo in the FAS

5. Comparison of per cent change in fasting apolipoprotein B-48 from baseline to month 6 between the olezarsen 80-mg treatment group and pooled placebo in the FAS

6. Comparison of per cent change in fasting non-high density lipoprotein cholesterol from baseline to month 6 between the olezarsen 80-mg treatment group and pooled placebo in the FAS

7. Comparison of per cent change in fasting triglycerides from baseline to month 12 between the olezarsen 50-mg treatment group and pooled placebo in the FAS

8. Comparison of percent change in fasting apolipoprotein C-III from baseline to month 6 between the olezarsen 50-mg treatment group and pooled placebo in the FAS

9. Comparison of percent change in fasting apolipoprotein C-III from baseline to month 12 between the olezarsen 50-mg treatment group and pooled placebo in the FAS

10. Comparison of proportion of patients who achieve ≥ 40% reduction in fasting triglycerides from baseline to month 6 between the olezarsen 50-mg treatment group and pooled placebo in the FAS

11. Comparison of percent change in fasting apolipoprotein B-48 from baseline to month 6 between the olezarsen 50-mg treatment group and pooled placebo in the FAS

12. Comparison of percent change in fasting non-high density lipoprotein cholesterol from baseline to month 6 between the olezarsen 50-mg treatment group and pooled placebo in the FAS

13. Comparison of the adjudicated acute pancreatitis event rate from week 1 to week 53 between the pooled olezarsen treatment group and pooled placebo in the subset of the FAS with a prior history of pancreatitis within 10 years prior to screening

14. Comparison of the adjudicated acute pancreatitis event rate from week 1 to week 53 between the pooled olezarsen treatment group and pooled placebo in the FAS

15. Comparison of the adjudicated acute pancreatitis event rate from week 13 to week 53 between the pooled olezarsen treatment group and pooled placebo in the subset of the FAS with a prior history of pancreatitis within 10 years prior to screening

16. Comparison of the adjudicated acute pancreatitis event rate from week 13 to week 53 between the pooled olezarsen treatment group and pooled placebo in the FAS

17. Comparison of the proportion of patients who achieve ≥ 70% reduction in fasting triglycerides from baseline to month 6 between the olezarsen 80-mg treatment group and pooled placebo in the FAS

18. Comparison of percent change in fasting non-high density lipoprotein cholesterol from baseline to month 12 between the olezarsen 80-mg treatment group and pooled placebo in the FAS

19. Comparison of the percent change in fasting apolipoprotein B-48 from baseline to month 12 between the olezarsen 80-mg treatment group and pooled placebo in the FAS

20. Comparison of the proportion of patients who achieve fasting triglycerides ≤ 880 mg/dL at month 6 between olezarsen 80-mg treatment group and pooled placebo in the FAS

21. Comparison of proportion of patients who achieve ≥ 70% reduction in fasting triglycerides from baseline to month 6 between the olezarsen 50-mg treatment group and pooled placebo in the FAS

22. Comparison of percent change in fasting non-high density lipoprotein cholesterol from baseline to month 12 between olezarsen 50-mg treatment group and pooled placebo in FAS

23. Comparison of percent change in fasting apolipoprotein B-48 from baseline to month 12 between the olezarsen 50-mg treatment group and pooled placebo in the FAS

24. Comparison of proportion of patients who achieve fasting triglycerides ≤ 880 mg/dL at month 6 between the olezarsen 50-mg treatment group and pooled placebo in the FAS

25. Comparison of adjudicated acute pancreatitis event rate from week 1 to week 53 between the pooled olezarsen treatment group and pooled placebo in the subset of the FAS with ≥ 2 events of adjudicated acute pancreatitis in the 5 years prior to enrollment

26. Comparison of the adjudicated acute pancreatitis event rate from week 13 to week 53 between the pooled olezarsen treatment group and pooled placebo in the subset of the FAS with ≥ 2 events of adjudicated acute pancreatitis in the 5 years prior to enrollment

27. Comparison of the proportion of patients who achieve fasting triglycerides ≤ 500 mg/dL at the primary analysis time point between the olezarsen 80-mg treatment group and pooled placebo in the FAS

28. Comparison of the proportion of patients who achieve fasting triglycerides ≤ 500 mg/dL at the primary analysis time point between the olezarsen 50-mg treatment group and pooled placebo in the FAS

Additional/exploratory outcomes:

For this application, PROMIS 29+2 was used to assess HRQoL, and PGIC was used to assess patient-reported outcomes.

- Patient-reported abdominal pain, other FCS-related symptoms (physical fatigue, difficulty thinking and diarrhea), diet, and impacts, health-related quality of life (HRQoL), pain interference, and cognitive function
- Emergency room (ER) visits, incidence of all-cause hospitalizations and total inpatient days

Safety

- Safety and tolerability assessments included adverse events, clinical laboratory tests, ECGs, use of concomitant medications, and independently adjudicated event rates of MACE for olezarsen as compared with placebo. These safety outcomes were included in this application.
- Independently adjudicated pancreatitis events were evaluated as an efficacy endpoint.

Anti-Drug Antibodies

- Samples were to be collected for immunogenicity assessment according to the study protocol at Baseline (Day 1 predose), during treatment, and during post treatment follow-up, including at early termination visits. These samples were tested for anti-olezarsen

	antibodies (ADA), and both sample-level and patient-level analyses were performed. **Pharmacokinetics** • During the Treatment Period (at the time points shown in the study protocol), blood samples were collected prior to dosing and at 2 and 4 hours post-dose for the determination of plasma olezarsen concentrations (measured as total full-length oligonucleotides or olezarsen equivalents, i.e., fully conjugated, partially conjugated, and unconjugated olezarsen).
Analysis method	For the primary endpoints, the percent change from Baseline to the primary analysis time point in fasting TG was compared between each olezarsen treatment group versus pooled placebo using an analysis of covariates (ANCOVA) model in the Full Analysis Set. The ANCOVA model included the effects of treatment (Olezarsen 80 mg, Olezarsen 50 mg, or Placebo), 2 randomization stratification factors (history of pancreatitis and previous treatment with volanesorsen), and log-transformed Baseline TG. The 95% confidence interval (CI) of the treatment differences was calculated using the robust variance estimator based on the Bell and McCaffrey method to account for potential heterogeneity in variance. Multiple imputation (MI) was used for missing values. For the 28 secondary endpoints, the methods were similar to those of the primary analysis (i.e., ANCOVA model in the Full Analysis Set), which were used to analyse secondary endpoints for the percent change in fasting lipid and apolipoprotein parameters (i.e., TG, apoC-III, apoB-48, non-HDL-C) from Baseline to Month(s) 6 and/or 12. For responder analyses (i.e., proportion of patients who achieved a percent reduction [i.e., ≥ 40% or ≥ 70% reduction] from Baseline or reduction below a threshold [i.e., ≤ 880 mg/dL or ≤ 500 mg/dL] in fasting TG to Month 6 or 12 in the Full Analysis Set), the applicable olezarsen treatment group was compared with the placebo group using a logistic regression model with the treatment group, history of pancreatitis (yes/no), previous treatment with volanesorsen (yes/no) as the factors, and log-transformed Baseline TG as a covariate. Missing TG values were imputed using the same MI method as the primary analysis of the primary endpoint. For analyses comparing adjudicated pancreatitis event rates, rates were compared between pooled olezarsen treatment group and placebo group using a Poisson regression model or Negative Binomial regression model with the treatment group, history of pancreatitis (yes/no), previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment as a covariate. The logarithm of time in years that each patient observed during the corresponding analysis period (Week 13 to Week 53 or Week 1 to Week 53/ET) was used as an offset variable.

	For additional/exploratory endpoints, methods similar to that of the primary analysis (i.e., ANCOVA model in the Full Analysis Set) were used to analyse exploratory endpoints.
Subgroup analyses	A prespecified subgroup analyses were conducted on the primary efficacy endpoint (mean percent change in fasting TG from Baseline at Month 6) by gender, age group, prior history of pancreatitis within 10 years of Screening, previous treatment with volanesorsen, location of study sites (US vs. non-US), region, race, ethnicity, diabetic status, and Baseline TG levels (< median vs. > median). The confidence intervals were not adjusted for multiplicity and therefore cannot be interpreted as hypothesis tests. The primary analysis time point (6 Months) was defined as the average of Weeks 23, 25, and 27. If 1 or 2 of the 3 assessments were missing, then non-missing assessments were used. The ANCOVA model included precent change from Baseline to the primary analysis time point in fasting TG as dependent variable, treatment group, the randomization stratification factor, prior history of pancreatitis within 10 years prior to Screening (yes vs. no) as the fixed effect and log-transformed baseline TG as a covariate. The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method. The Shapiro-Wilk test was used to assess normality. A non-prespecified subgroup analyses and ad hoc analyses were conducted on the average percentage change from baseline in fasting triglycerides from week 1 through week 53, olezarsen 80 mg and olezarsen 50 mg, versus placebo. The population included participants in the olezarsen group 80mg and 50 mg, who had prior to the Balance trial received volanesorsen treatment, compared to participants in the placebo group. The confidence intervals were not adjusted for multiplicity and therefore cannot be interpreted as hypothesis tests. Patients with no post-Baseline data (or after Week 13) were excluded from the analysis. Average percent change from Baseline in fasting TG levels equals the area under the concentration-time curve (AUC) of TG percent change divided by days of the corresponding treatment period. The least-squares mean (LSMs) and their 95% CI were estimated from an ANCOVA model with treatment group and 2 randomization stratification factors, prior history of pancreatitis within 10 years prior to screening (yes vs. no), previous treatment with volanesorsen (yes vs. no) as the fixed effects and log-transformed Baseline TG as a covariate. The 95% CIs of treatment difference and p-values were calculated using the robust variance estimator based on the Bell and McCaffrey method.
Other relevant information	*No*

Appendix B. Results for Clinical effectiveness per Study

The key results of the pivotal clinical study, Balance, are described in Table 55 below.

Table 55. Results per study

Results from Balance (NCT04568434)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*p*-value	Difference	95% CI	*p*-value		
Fasting triglyceride levels at 6 months (percentage change compared to baseline)	80 mg olezarsen	22	-31.99 (-49.031, -14.940)	−43.5 percentage points	−69.1, −17.9	p<0.001	N/A	N/A	N/A	The fasting TGs were compared between each olezarsen treatment group versus the pooled placebo using an analysis of covariates (ANCOVA) model in the Full Analysis Set. The 95% confidence interval (CI) of the treatment differences was calculated using the robust variance estimator based on the Bell and McCaffrey method to account for potential heterogeneity in variance. Multiple	Balance trial publication (2024) and Tryngolza® EPAR [1, 43]
	placebo	23	11.52 (-5.321, 28.356)								
	50 mg olezarsen	21	-10.85 (-27.797, 6.095)	-22.37 percentage points	-47.200, -2.463	p = 0.08	N/A	N/A	N/A		Balance trial publication (2024) and Tryngolza® EPAR [1, 43]
	placebo	23	11.52 (-5.321, 28.356)								

Results from Balance (NCT04568434)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*p*-value	Difference	95% CI	*p*-value		
										imputation was used for missing values.	
Fasting triglyceride levels at 12 months (percentage change compared to baseline)	80 mg olezarsen	22	-38.50 (-58.187, -18.815)	-59.4%	-90.7, -28.1	p= 0.0002	N/A	N/A	N/A	ANCOVA model in the Full Analysis Set. The olezarsen treatment group was compared with the placebo group using a logistic regression model with the treatment group, history of pancreatitis (yes/no), previous treatment with volanesorsen (yes/no) as the factors, and log-transformed Baseline TG as a covariate. Missing TG values were imputed using the same MI method as the primary analysis of the primary endpoint.	Balance trial publication (2024) and Tryngolza® EPAR [1, 43]
	placebo	23	20.89 (1.016, 40.764)								
	50 mg olezarsen	21	-22.92 (-42.505, -3.336)	-43.8%	-73.9, -13.7	p= 0.0044	N/A	N/A	N/A		Balance trial publication (2024) and Tryngolza® EPAR [1, 43]
	placebo	23	20.89 (1.016, 40.764)								
Episodes of acute	80 mg olezarsen	43	4.37 (0.942, 20.298)	-31.94	N/A	N/A	Mean rate ratio: 0.12	(0.02, 0.66)	0.0144	The adjudicated pancreatitis event rates	Balance trial

Results from Balance (NCT04568434)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis method	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*p*-value	Difference	95% CI	*p*-value		
pancreatitis at week 53 (mean event rate/100 patient years)										were compared between pooled olezarsen treatment group and placebo group using a Poisson regression model or Negative Binomial regression model with the treatment group, history of pancreatitis (yes/no), previous treatment with volanesorsen (yes/no) as the factors, and number of adjudicated acute pancreatitis events in 5 years prior to the enrollment as a covariate. The logarithm of time in years that each patient observed during the corresponding analysis.	publication (2024) and Tryngolza® EPAR [1, 43]
	50 mg olezarsen										
	placebo	23	36.31 (14.700, 89.685)								

Appendix C. Subsequent Treatment

N/A. There were no subsequent treatments in the head-to-head Balance study, nor are patients expected to receive subsequent treatment, as FCS is a chronic disease that entails lifelong treatment.

Appendix D. Comparative Analyses

N/A. As the pivotal trial Balance is a head-to-head study, this section is not applicable.

Table 56. Comparative analysis of studies comparing [intervention] with [comparator] for patients with [indication]

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	p-value	Difference	CI	p-value		
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Appendix E. Extrapolation of Patient Transitions

E.1 Parametric Extrapolation Models - N/A

Not applicable.

E.1.1 Extrapolation of [Clinical Outcome 1]

E.1.1.1 Log-Cumulative Hazard Plots and Residual Plots

E.1.1.2 Internal validity

E.1.1.2.1 Assessment of Statistical and Visual Fit (AIC and BIC)

E.1.1.2.2 Assessment of Smoothed Hazard Functions

E.1.1.3 External Validity

E.1.1.4 Other Assumptions

E.1.2 Extrapolation of [Clinical Outcome 2]

E.2 Transition Probabilities

Table 57. Transition matrix for olezarsen 0-3 months

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs<500 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 58 Transition matrix for olezarsen 3-6 months

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs<500 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 59 Transition matrix for olezarsen 6-12 months

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs<500 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 60 Transition matrix olezarsen 1-2 years

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs<500 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 61 Transition matrix olezarsen 2+ years

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs<500 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 62. Transition matrix for SoC 0-3 months

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs<500 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead AP	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX	XXXX

Table 63 Transition matrix for SoC 3-6 months

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs<500 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 64 Transition matrix for SoC 6-12 months

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs<500 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 65 Transition matrix SoC 1-2 years

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs<500 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 AP naïve	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 66 Transition matrix SoC 2+ years

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs<500 AP naïve	[redacted]													
TGs 500<880 AP naïve	[redacted]													
TGs 880<2,000 AP naïve	[redacted]													
TGs≥2,000 AP naïve	[redacted]													
TGs<500 1 AP	[redacted]													
TGs 500<8	[redacted]													

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
80 1 AP														
TGs 880<2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs≥2,000 1 AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs<500 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 500<880 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TGs 880<2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Off/On	TGs<500 AP naïve	TGs 500<880 AP naïve	TGs 880<2,000 AP naïve	TGs≥2,000 AP naïve	TGs<500 1 AP	TGs 500<880 1 AP	TGs 880<2,000 1 AP	TGs≥2,000 1 AP	TGs<500 Rec AP	TGs 500<880 Rec AP	TGs 880<2,000 Rec AP	TGs≥2,000 Rec AP	CP	Dead AP
TGs≥2,000 Rec AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
CP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dead AP	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

E.2.1 Internal Validity

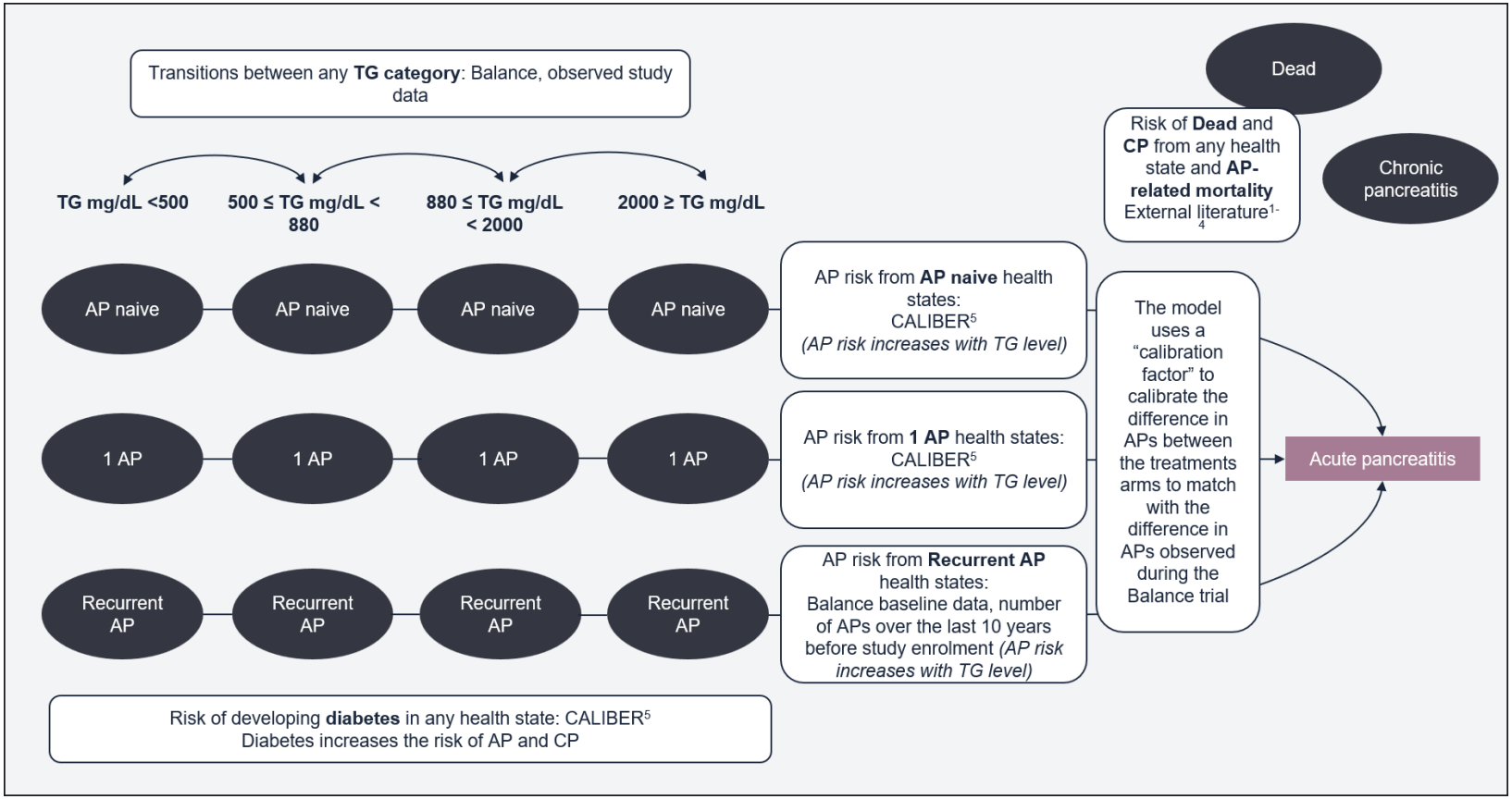
The indirect treatment effect on AP of olezarsen mediated through TG levels and AP history, according to the above approach, does not fully capture the impact of olezarsen on AP risk. This is due to several factors, one of which is that an improvement in TG level does not always lead to a change in health state, since each health state spans a range of TG levels. Furthermore, the lack of AP observations in the AP naïve and 1 AP patients necessitated the use of CALIBER, which may have underestimated the effect on AP.

The mean pancreatitis event rate per 100 patient years in Balance was 4.37 for the olezarsen group (50 mg and 80 mg combined) and 36.31 for the placebo group, resulting in a mean rate ratio of 0.12 [38, 58]. The application of the calibration factors maintains this mean rate ratio over the model's time horizon. Therefore, to derive the treatment effect observed in Balance, calibration factors are used to adjust the rate ratio between the treatment arms [59, 60]. Thus, model directly incorporates the mean AP rate ratio (0.12) observed in the Balance study for the first year, ensuring that the short-term treatment effect aligns with empirical trial results, potentially strengthen the model's internal validity. The model also includes the option of excluding the calibration factor. When turning off the calibration factor the same risk (i.e., the risk observed in the Balance study) of developing an AP is applied to all health states.

Further, as stated in section 9.1, subjects in the Balance study were only followed for one year. Therefore, external data was used for long-term complications as presented in Table 19. External data was also used to estimate the risk of an AP event for patients in the AP naïve and 1 AP health states as no patients in these health states had an AP event in the Balance study.

Figure 16 presents a detailed description of the data used in the model.

Figure 16 Description of data included in the model



Abbreviations: AP, acute pancreatitis; CP, chronic pancreatitis; TG, triglyceride.

E.2.2 External Validity

FCS is a rare disease, which may limit the availability of robust long-term evidence and makes it challenging to validate clinically relevant outcomes and transition probabilities against independent data sources. However, the structure and assumptions of the model are informed by a previous cost-effectiveness model in the same disease area, which was accepted for decision-making by both TLV in Sweden and NICE in the UK [46, 47]. While this does not eliminate uncertainty around the external validity of the current model, it provides support for the relevance and acceptability of the modelling approach in comparable health technology assessment settings.

The model health states are based on TG levels and history of AP. Change in TG levels was the primary endpoint of the Balance trial. Change in TG levels has been shown to have a relationship with APs and CPs which are clinically relevant outcomes in patients with FCS [4, 5]. The model also captures that increasing risk of AP and CP with elevated TG levels, through the 4 TG health states. Studies has also shown that an history of AP increased the risk of AP and CP, something that the model also captures [4, 11, 22]. Thus, the model is built to accurately present the natural history of FCS.

E.2.3 Other Assumptions

The prevalence of diabetes in the model is capped at levels reported by literature, as presented in Table 67.

Table 67 Peak prevalence of diabetes

Health state		Prevalence	Source
AP Naïve	TGs < 500	5.2%	Scherer et al., 2014: In the National Health and Nutrition Examination Survey (NHANES) study, the prevalence of diabetes in US adults with normal TG level was 5.2% and in those with TG levels between 500-2000 mg/dl was 14.6% [77]
	TGs 500 < 880	14.6%	
	TGs 880 < 2,000	14.6%	
	TGs ≥ 2,000	20.0%	In the >22.6 AP naïve health state, in the absence of data in this category, prevalence is assumed to peak at 20%
1 AP	TGs < 500	5.2%	Scherer et al., 2014: In the NHANES study, the prevalence of diabetes in US adults with normal TG level was 5.2% and in those with TG levels between 500-2000 mg/dl was 14.6%. [77]
	TGs 500 < 880	14.6%	
	TGs 880 < 2,000	14.6%	

	TGs ≥ 2,000	23.0%	Das et al., 2013: prevalence of diabetes was 23% after one episode of AP[78]
recurrent AP	TGs < 500	5.2%	Scherer et al., 2014: In the NHANES study, the prevalence of diabetes in US adults with normal TG level was 5.2% and in those with TG levels between 500-2000 mg/dl was 14.6% [77]
	TGs 500 < 880	14.6%	
	TGs 880 < 2,000	14.6%	
	TGs ≥ 2,000	72.0%	Fortson et al., 1995: The prevalence of diabetes was 72% in patients with ultra-high TG pancreatitis (mean 4567mg/dL)[79]
CP	N/A	80.0%	NICE, 2018 [80]

Appendix F. Serious Adverse Events

Serious adverse events with a frequency of ≥ 1% that were observed in the Balance study are reported below in Table 68.

Table 68 Serious adverse events reported with a frequency of ≥1% from the Balance trial

Preferred term	Placebo (n = 23)	Olezarsen 50 mg (n = 21)	Olezarsen 80 mg (n = 22)
Patients with at least one Serious TEAE, n (%)	9 (39.1)	4 (19.0)	3 (13.6)
Gastrointestinal disorders			
Gastric varices	1 (4.3)	0	0
Gastric varices haemorrhage	1 (4.3)	0	0
Gastritis	1 (4.3)	0	0
Intestinal perforation	0	0	1 (4.5)
Pancreatitis	4 (17.4)	1 (4.8)	1 (4.5)
Pancreatitis acute	3 (13.0)	0	0
Pancreatitis necrotizing	2 (8.7)	0	0
General disorders and administration site conditions			
Sudden death	0	1 (4.8)	0
Hepatobiliary disorders			
Cholangitis	1 (4.3)	0	0
Hepatic cirrhosis	0	0	1 (4.5)
Infections and infestations			

Cellulitis	1 (4.3)	0	0
Gastroenteritis bacterial	0	1 (4.8)	0
Injury, poisoning and procedural complications			
Intentional overdose	0	1 (4.8)	0
Metabolism and nutrition disorders			
Hypoglycaemia	1 (4.3)	0	0
Hyponatraemia	1 (4.3)	0	0
Pancreatogenous diabetes	1 (4.3)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of the oral cavity	1 (4.3)	0	0

Appendix G. Health-Related Quality of Life

G.1 Data Collection – Overview of Response

N/A, data presented in 10.2.

G.2 Reporting of Domains

The PROMIS-29+2, a fixed-form profile HRQoL measure adapted from a reduced set of PROMIS items (depression, anxiety, physical function, pain interference, fatigue, sleep disturbance, cognition, and ability to participate in social roles and activities). The PROMIS-Preference measure (PROPr; a health utility measure) can be derived from the PROMIS-29+2 instrument, generating utilities directly, and the PROPr can in turn be mapped to EQ-5D utility values.

The PROPr score (presented in Table 39. Results for PROMIS 29 +2 (PROPr) olezarsen 50 mg and Table 40 Results for PROMIS 29 +2 (PROPr) olezarsen 80 mg) was be calculated as [1, 9]:

- summing the values of the response to each question to get a raw total score for each domain. If more than 50% of the questions in a domain were missing, the domain score was to be considered as missing for the visit. If less than or equal to 50% of the questions in a domain were missing, the missing items will be imputed using the average of the non-missing items in the same domain and rounded to the nearest integer.
- converting the raw domain scores to T-scores using the PROMIS scoring manual. A T-score of 50 is the average of the United States general population. Higher symptom scores indicate increased symptom burden and higher function scores indicate better functioning.

The T-score for each PROMIS-29+2 domain are presented below.

Table 69 Exploratory Analysis PROMIS 29+2 Profile v2.1 Domain Scores at Month 6 and 12

	Statistic	Placebo (N=23)	Olezarsen 50 mg (N=21)	Olezarsen 80 mg (N=22)
Physical Function				
Baseline				

Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Depression				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue				
Baseline	[redacted]	[redacted]	[redacted]	[redacted]

	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Pain interference	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]
Sleep disturbance	[redacted]	[redacted]	[redacted]	[redacted]
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]

Ability to participate in Social Roles and activities				
Baseline				
Month 6				
Month 12				
Cognitive function abilities				
Baseline				
Month 6				
Month 12				

Abbreviation: n, number of observations; SD, standard deviation; SEM, standard error of the mean

Figure 17. PROMIS 29 + 2 Profile per domain placebo



Figure 18. PROMIS 29 + 2 Profile per domain olezarsen 50 mg



Figure 19. PROMIS 29 + 2 Profile per domain olezarsen 80 mg



G.3 Mapping

The mapping from PROMIS to Danish EQ-5D-5L HSUVs were conducted through two algorithms.

G.3.1 PROMIS to EQ-5D-3L

The PROMIS utility values, PROPr, can be directly mapped to EQ-5D-3L using a recently published mapping algorithm by Tang et al [71]. UK EQ-5D-3L values were derived from the PROMIS domain scores following the recommended mapping approach for obtaining EQ-5D preference scores for any value set described in Tang et al. (Table 6). Values for each EQ-5D domain were obtained by multiplying the Tang et al. indirect mapping reduced regression model coefficients (see Tang Table 2) by patients' PROMIS domain scores. Then, the cut-off points given in the Tang et al. regression results (see Tang Table 2) were applied to attribute a 1-5 EQ-5D level for each domain, yielding individual EQ-5D-3L item responses for every patient. The individual EQ-5D-5L item responses were then cross-walked to EQ-5D-3L index scores using the NICE Decision Support Unit "eq5dmap" algorithm with patient age and gender as covariates[81].

The mapped EQ-5D-3L utility values by arm over time are presented in Table 70.

Table 70. Mean EQ-5D-3L by time point

Treatment Arm	Observation	Mean	SE	95% CI
[redacted]				

Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olezarsen 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olezarsen 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olezarsen 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olezarsen 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olezarsen 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Olezarsen 80 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The predicted HSUVs (EQ-5D-3L) based on OLS 19 (see G.4) are presented in Table 71.

Table 71 HSUVs EQ-5D-3L UK

AP History	TG Health State	Predicted value (EQ-5D-3L UK)
AP Naïve	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
1 AP	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
Recurrent AP	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]

[redacted] [redacted]

G.3.2 EQ-5D-3L UK to EQ-5D-5L DK

The estimated EQ-5D-3L utilities based on the UK tariff were converted to Danish EQ-5D-5L utilities using the mapping approach described by Torkilseng et al [72]. In the study, a simple linear algorithm was developed from a large, pooled dataset of 11 oncology clinical trials and externally validated in three separate oncology datasets, with a largest absolute prediction error of 0.020 across observed UK EQ-5D-3L mean utilities ranging from 0.628 to 0.835. In the absence of validated alternatives for adjusting published mean UK EQ-5D-3L utilities to reflect Danish EQ-5D-5L preferences, use of this approach is considered appropriate for the present analysis and preferable to using unadjusted UK EQ-5D-3L values, which may increase decision uncertainty. Although the algorithm was developed using oncology data only, the authors note that it may still be considered outside oncology with appropriate caution, while acknowledging that further validation is needed in other disease settings. Further, we argue that the relationship is between value sets, not disease biology, and thus driven by differences in tariffs and instrument structure (3L vs 5L) and should be transferable.

The used algorithm follows:

$$: \mu DK_5L = 0.231 + \mu UK_3L \times 0.773$$

where

- $\mu_i(DK_5L_i)$ is the mean EQ-5D-5L utility value on the Danish tariff,
- $\mu_i(UK_3L_i)$ is the mean EQ-5D-3L utility value on the UK tariff,
- 0.231 is an intercept coefficient,
- 0.773 is a slope coefficient. This can also be used to calculate the standard error.

The estimated EQ-5D-5L DK HSUVs are presented in Table 42.

G.4 Calculation of Utility Values

OLS 19 is presented in the tables below. The equation for OLS 19 can be notionally represented in a simplified form as:

$$y_i = \alpha + \beta \cdot AP\ category + \beta \cdot TG\ category$$

Note that the trial utilities from OLS 19 were modified before application in the model to account for the very high utility of the <880 mg/dL AP naïve reference value (1.067), which was higher than that of the UK age and gender adjusted general population (0.855). A multiplier of 0.801 was therefore applied to all trial utilities derived using OLS 19 within the economic model.

Table 72. Models attempted for the regression analyses

Model	Covariates and details
OLS 19	Utilities (dependent variable) and TG categories (<880, 880<2000, 2000+) and AP categories (AP Naïve, 1 AP, 2+ AP); All timepoints pooled

Abbreviations: AP, acute pancreatitis; EQ-5D, EuroQol 5-Dimension; OLS, Ordinary Least Squares; TG, triglyceride

Table 73 OLS 19 summary

Baseline Utility	Coef.	Std. Error	t	P > t	95% CI
AP Category					
3 (ref. group)	Ref	Ref	Ref	Ref	Ref
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TG Category					
1 (ref. group)	Ref	Ref	Ref	Ref	Ref
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Intercept	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: ref, reference, Coef., coefficient, Std. Error, standard error, CI, confidence interval

Table 74. Outputs from the OLS analysis of the mapped EQ-5D utility values at all timepoints (model OLS 19)

EQ-5D	Coefficient	SE	Z	P > z	[95% CI]	
TG category						
880<2000	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2000+	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AP category						
1 AP						
2+ AP						
Intercept						

G.5 Detailed PGIC data

The tables below presents the detailed PGIC data.

Table 75 Results for PGIC Olezarsen 50 mg

	Intervention / Olezarsen 50 mg (n=21)					Comparator / Placebo (n=23)				
	Much Better	A Little Better	No Change	A Little Worse	Much Worse	Much Better	A Little Better	No Change	A Little Worse	Much Worse

PGIC = Patient Global Impression of Change

Note: Percentages were based on the number of available patients at each visit in each treatment group.

Table 76 Results for PGIC Olezarsen 80 mg

	Intervention / Olezarsen 80 mg (n=22)					Comparator / Placebo (n=23)				

	Intervention / Olezarsen 80 mg (n=22)					Comparator / Placebo (n=23)				

PGIC = Patient Global Impression of Change

Note: Percentages were based on the number of available patients at each visit in each treatment group

Appendix H. Literature Searches for the Clinical Assessment

N/A. As the pivotal trial Balance is a head-to-head study, this section is not applicable.

H.1 Effect and Safety of the Intervention and Comparators

N/A.

Example of table. Bibliographic databases

Database	Platform/Website	Date of search
N/A	N/A	N/A

Example of table. Other sources

Source	Website	Search strategy/ keywords used	Date of search
N/A	N/A	N/A	N/A

H.2 Systematic Selection of Studies and References

N/A.

Table 77. Inclusion and exclusion criteria [may be deleted/replaced]

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Modification, local adaptation
Population	N/A	N/A	N/A
Intervention	N/A	N/A	N/A
Comparators	N/A	N/A	N/A
Outcome	N/A	N/A	N/A
Study design/ publication type	N/A	N/A	N/A
Limitations, e.g. language	N/A	N/A	N/A

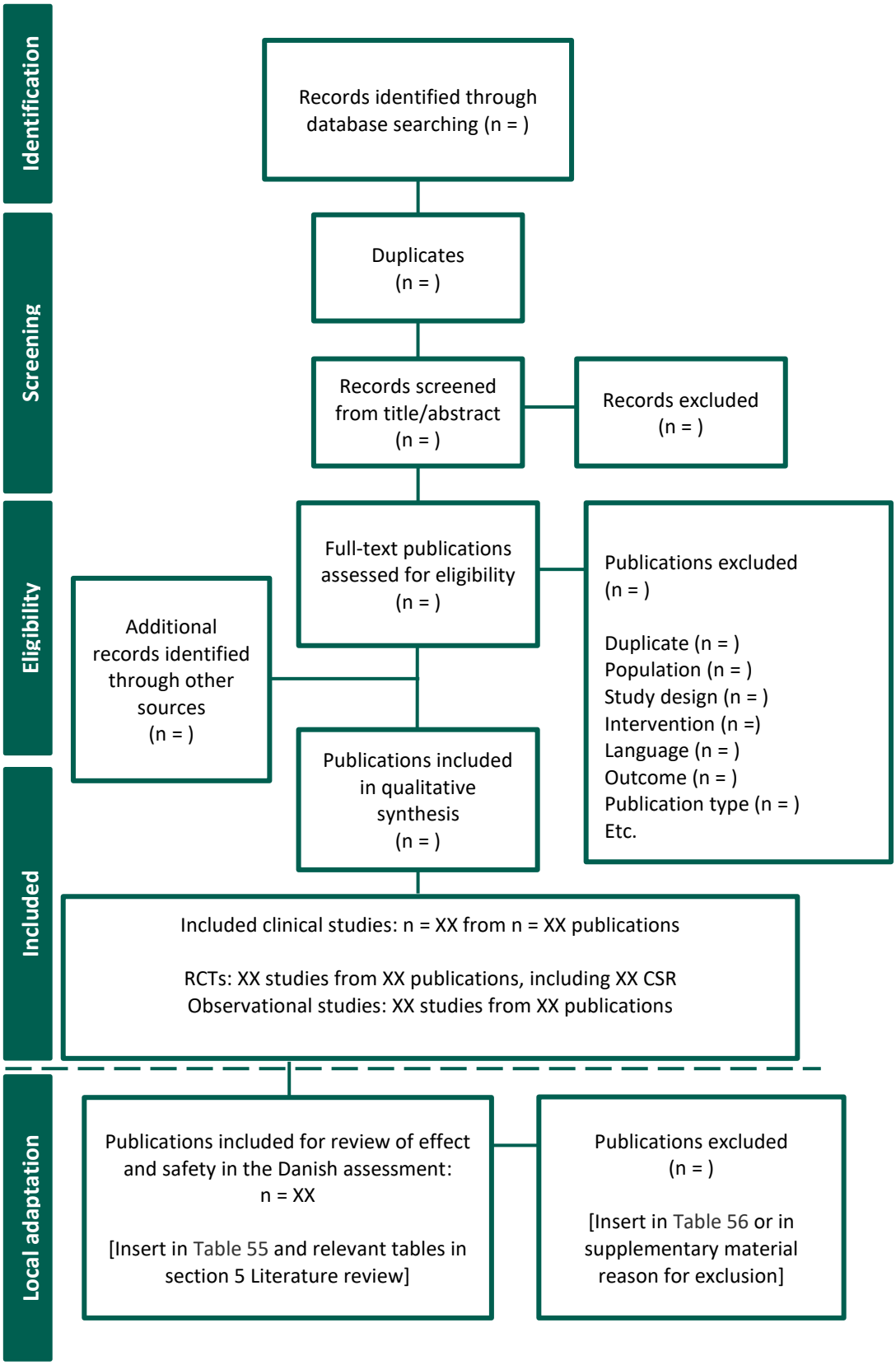

Identification
Screening
Eligibility
Included
Local adaptation
Records identified through database searching (n =)
Duplicates (n =)
Records screened from title/abstract (n =)
Records excluded (n =)
Full-text publications assessed for eligibility (n =)
Publications excluded (n =)
Duplicate (n =)
Population (n =)
Study design (n =)
Intervention (n =)
Language (n =)
Outcome (n =)
Publication type (n =)
Etc.
Additional records identified through other sources (n =)
Publications included in qualitative synthesis (n =)
Included clinical studies: n = XX from n = XX publications
RCTs: XX studies from XX publications, including XX CSR
Observational studies: XX studies from XX publications
Publications included for review of effect and safety in the Danish assessment: n = XX
[Insert in Table 55 and relevant tables in section 5 Literature review]
Publications excluded (n =)
[Insert in Table 56 or in supplementary material reason for exclusion]

Table 78. Studies/references included in the Danish assessment

	Reference(s)
Study 1	N/A
Study 2	N/A

Table 79. Excluded studies/references [may alternatively be submitted as supplementary material]

	Reference(s)
Study 1	N/A
Study 2	N/A

Appendix I. Literature Searches for Health-Related Quality of Life

I.1 Systematic Search

N/A

I.2 Focused Search

N/A

Appendix J. Literature Searches for Additional Inputs to the Health Economic Model

J.1 Systematic Search

N/A

J.2 Focused Search

N/A

Appendix K. Justification for Confidential Information

Table 80. Justification for confidential information

Parameter	Justification
Average dose of olezarsen in the Balance study, compliance rate, number of patients with dose reduction, and information about the patient that had a dose reduction.	The redacted information relates to detailed treatment utilisation patterns observed in the Balance study, including average dose intensity, compliance, dose modifications, and individual patient-level characteristics associated with dose reductions. These data have not been published and provide detailed insight into expected treatment intensity and medicine consumption beyond the information currently available in public sources. Public disclosure would enable third parties, including competitors and stakeholders in other healthcare systems, to derive assumptions regarding treatment duration, effective dose intensity, medicine utilisation, and expected drug consumption. Such information could influence future pricing, reimbursement, and procurement discussions in jurisdictions outside Denmark and could reduce the commercial value of the company's proprietary clinical evidence package.
Number of patients that discontinued study drug and reason for discontinuation if that is not published.	The requested information contains unpublished study-level information regarding treatment discontinuations and underlying reasons for discontinuation that are not fully disclosed in public sources.

Parameter	Justification
	Public disclosure would reveal detailed treatment persistence and discontinuation patterns that may be used by external stakeholders to predict long-term treatment duration and expected medicine utilisation in clinical practice. Such information may be relevant for future reimbursement assessments, budget impact analyses, and market access discussions in other jurisdictions. Disclosure would therefore be expected to adversely affect the company's commercial interests outside the present Danish assessment.
Number and proportion of patients with missing measurements for each outcome reported in this application.	The requested information concerns detailed data regarding missing assessments for individual study endpoints. These data have not been published and form part of the sponsor's proprietary clinical development package. Public disclosure would reveal information regarding study conduct, data completeness, and analytical robustness that has not been made available through scientific publications or regulatory documents. The information therefore retains commercial value as part of the overall evidence package supporting the product and future global scientific and market access activities.
Severe AEs reported in the Balance study representing grade ≥ 3 AEs.	The confidentiality request relates only to unpublished grade ≥3 adverse event data that are not included in publicly available regulatory documents. These detailed safety analyses form part of the sponsor's proprietary clinical evidence package and provide a more granular characterisation of the safety profile than is currently available in public sources. Public disclosure of unpublished safety analyses could affect the company's ability to determine the timing, context, and interpretation of future scientific communications and publications and could be used by competitors or external stakeholders before full publication and scientific peer review of the data
Number of patients that had a dose reduction due to AE in the Balance study.	The number of patients requiring dose reduction due to adverse events constitutes unpublished treatment management information from the Balance study. These data provide detailed insight into treatment tolerability, treatment intensity, and expected drug utilisation and have not been published. Public disclosure would facilitate more precise estimation of treatment consumption and treatment management patterns by external parties and could influence future health economic assessments, market analyses, and reimbursement evaluations in other countries. The

Parameter	Justification
	information is therefore considered commercially sensitive.
Transition probabilities	The confidentiality request applies only to transition probabilities derived from unpublished patient-level analyses conducted using Balance data. These transition probabilities are generated through proprietary analytical methods and constitute a key component of the sponsor's economic modelling framework. Public disclosure would reveal elements of the company's modelling methodology and analytical approach that may be reused in future reimbursement submissions across multiple jurisdictions. Disclosure would enable third parties to replicate or closely approximate proprietary modelling outputs, thereby reducing the commercial value of the company's investment in model development and evidence generation
Expected number of eligible patients in Denmark to receive Tryngolza®	The estimate of the expected number of eligible patients in Denmark combines epidemiological evidence, market intelligence, and validation by Danish clinical experts. The resulting estimate reflects the company's assessment of the addressable patient population and anticipated market opportunity. Public disclosure would reveal commercially sensitive market assumptions and forecasts that are used for strategic planning and market access activities. Competitors and other external stakeholders could use this information to gain insight into the company's commercial expectations and market forecasts. The information is therefore considered commercially sensitive
Frequency of resource use	The resource utilisation estimates are based on unpublished information obtained from the Balance clinical study report and unpublished information generated during external HTA processes. These estimates represent proprietary evidence supporting the economic evaluation and have not been publicly disclosed. Public disclosure would reveal detailed assumptions regarding healthcare resource consumption and cost drivers underpinning the value proposition of Tryngolza. Because these assumptions may be used in future reimbursement submissions and negotiations across multiple jurisdictions, disclosure would adversely affect the company's commercial

Parameter	Justification
	interests by reducing the exclusivity of its proprietary evidence package.
Result	The confidentiality request does not relate to the concepts of ICERs, QALYs or LYs themselves, but to the specific results generated using confidential model inputs and assumptions. The model incorporates commercially sensitive information, including unpublished clinical data, proprietary transition probabilities, confidential epidemiological assumptions, treatment utilisation assumptions, and market-specific inputs. Public disclosure of the resulting ICERs, QALYs, and LYs would reveal the commercial value attributed to the product under a specific set of confidential assumptions and could permit inferences regarding underlying confidential model inputs. Furthermore, publication of these outcomes could influence future reimbursement negotiations, pricing discussions, and health economic assessments in other jurisdictions where reimbursement processes are ongoing or anticipated. Disclosure would therefore be expected to adversely affect the company's commercial interests outside the current Danish assessment.
HRQoL	Unpublished analyses or results that have not been publicly disclosed and that form part of the sponsor's proprietary evidence package intended for future scientific and market access activities are confidentially marked

Appendix L. Other

Olezarsen - Discovered by Ionis Pharmaceuticals, Inc

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