# Long-term effects of volanesorsen on triglycerides and pancreatitis in patients with familial chylomicronaemia syndrome (FCS) in the UK Early Access to Medicines Scheme (EAMS)

Alan Jones [a,*], Katherine Peers [a], Anthony S. Wierzbicki [b], Radha Ramachandran [b], Michael Mansfield [c], Charlotte Dawson [d], Antonio Ochoa-Ferraro [d], Handrean Soran [e], Fiona Jenkinson [f], Ian McDowell [g], Paul Downie [h], Paul Hamilton [i], Richard D Jones [j]

[a] Birmingham Heartlands Hospital, Bordesley Green East, Bordesley Green, Birmingham, West Midlands, B9 5SS, UK
[b] Guy's and St. Thomas' Hospital, Great Maze Pond, London, SE1 9RT, UK
[c] Leeds Teaching Hospitals, Beckett Street, Leeds, West Yorkshire, LS9 7TF, UK
[d] University Hospitals, Trust Headquarters, Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Edgbaston, Birmingham, West Midlands, B15 2GW, UK
[e] Manchester University, Cobbett House, Manchester University NHS Foundation Trust, Oxford Road, Manchester, M13 9WL, UK
[f] Royal Victoria Infirmary, Queen Victoria Rd, Newcastle upon Tyne, NE1 4LP, UK
[g] Cardiff University School of Medicine, Neuadd Meirionnydd, Cardiff, CF14 4YS, UK
[h] Salisbury District General Hospital, Odstock Rd, Salisbury, SP2 8BJ, UK
[i] Centre for Medical Education, Queen's University Belfast, 97 Lisburn Rd, Belfast, BT9 7BL, UK
[j] Akcea Therapeutics, St James House, 72 Adelaide Road, Dublin 2, D02 YO17, Ireland

## ABSTRACT

*Background and aims:* The VOL4002 study assessed the efficacy and safety of volanesorsen in 22 adults with genetically confirmed familial chylomicronaemia syndrome (FCS) treated in the UK Early Access to Medicines Scheme (EAMS), with ("prior exposure") or without ("treatment naive") previous treatment in the APPROACH and/or APPROACH-OLE volanesorsen phase 3 studies.

*Methods:* Data collection focused on triglyceride (TG) levels, platelet counts and pancreatitis events. Pancreatitis incidence during volanesorsen treatment was compared against the 5-year period preceding volanesorsen exposure. Volanesorsen 285 mg was self-administered subcutaneously once every 2 weeks.

*Results:* Individual patient volanesorsen exposure ranged from 6 to 51 months (total cumulative exposure, 589 months). Among treatment-naive patients (n = 12), volanesorsen treatment resulted in an averaged median 52% reduction (−10.6 mmol/L) from baseline (26.4 mmol/L) in TG levels at 3 months, which were maintained through time points over 15 months of treatment (47%–55% reductions). Similarly, prior-exposure patients (n = 10) experienced a 51% reduction (−17.8 mmol/L) from pre-treatment baseline (28.0 mmol/L), with reductions of 10%–38% over 21 months of treatment. A comparison of pancreatitis event rates found a 74% reduction from the 5-year period before (one event/2.8 years) and during (one event/11.0 years) volanesorsen treatment. Platelet declines were consistent with observations in phase 3 clinical trials. No patient recorded a platelet count $<50 \times 10^9$/L.

*Conclusions:* This longitudinal study supports the efficacy of volanesorsen in patients with FCS for lowering TG levels over treatment periods up to 51 months with no apparent safety signals related to increased duration of exposure.

## 1. Introduction

Familial chylomicronaemia syndrome (FCS) is an ultra-rare genetic disorder of lipid metabolism, affecting 3000 to 5000 individuals globally [1,2]. This disorder is characterised by severe elevations in triglyceride (TG) levels (>10 mmol/L; >885 mg/dL), carried predominantly in

chylomicrons [3]. FCS is caused by a marked reduction in or absence of lipoprotein lipase (LPL) activity. LPL is an enzyme that mediates the lipolysis of TGs in chylomicrons and TG-rich lipoproteins [4]. The genetic defect in FCS is attributed to inactivating mutations in both *LPL* gene alleles in about 80% of cases or in other genes including *APOC2*, *APOA5*, *GPIHBP1*, and *LMF1*, among others, that encode proteins required for LPL activity in about 20% of cases [5]. Chylomicronaemia-associated reductions in blood flow in the microcirculation cause a range of symptoms including recurrent episodes of abdominal pain, diarrhoea, impaired cognition ("brain fog"), and fatigue [6,7]. It has been previously hypothesized that a serious manifestation of reduced blood flow in the microcirculation may lead to high risk of acute pancreatitis. Repeated episodes of acute pancreatitis may result in exocrine and endocrine pancreatic insufficiency, are associated with substantial morbidity, and can be fatal [2,5]. Management of FCS requires limiting total fat intake to <10%–15% of daily calories or 15–20 g per day, which is burdensome for patients. Treatment with statins, fibrates, nicotinic acid, and fish oils is largely ineffective [2,5,8].

Volanesorsen, a 2′-O-(2-methoxyethyl)–modified antisense oligonucleotide molecule, reduces plasma TG levels through the inhibition of apoC-III via LPL-dependent and -independent pathways [9,10]. Volanesorsen received conditional European Union marketing authorisation in May 2019 as an adjunct to diet in adults with genetically confirmed FCS and at high risk for pancreatitis, in whom response to diet and TG-lowering therapy has been inadequate. The approved recommended dose is 285 mg subcutaneously once weekly for 3 months. After 3 months, dose frequency should be reduced to 285 mg every 2 weeks with further dose adjustment possible at subsequent 3-month intervals. In the United Kingdom, the Medicines and Healthcare Products Regulatory Agency granted early access to volanesorsen for the treatment of adults with FCS through an Early Access to Medicines Scheme (EAMS) on 20 March 2018 (EAMS 47857/0001) at a dose of 285 mg once every 2 weeks (a lower dose than that which was subsequently approved). The current study (VOL4002) was designed to describe the efficacy and safety of volanesorsen in patients with FCS who received volanesorsen through the UK EAMS.

## 2. Patients and methods

### 2.1. Study design and participants

Patients with FCS were enrolled into the volanesorsen EAMS programme upon completion of an Initial Application and Drug Supply Request by the prescribing physician. Following a review of the individual request and fulfilment of the program eligibility criteria, the study protocol, training, and relevant materials on posology and monitoring, and on the collection and reporting of adverse events (AEs), were provided. Written informed consent was provided by the study Sponsor and was received by all patients agreeing to participate. Volanesorsen was administered subcutaneously as a single 1.5-mL, 285-mg (equivalent to 300 mg volanesorsen sodium) injection once every 2 weeks. Recommended injection sites included the abdomen, thigh, and back of the upper arm. Volanesorsen administration was initiated through routine clinical practice in the hospital outpatient setting. Subsequent injections could be self-administered or administered by a caregiver following training from the lipid clinic staff, based on patient and physician preference. Patients returned to the lipid clinic for blood collection to monitor platelet counts at the frequency mandated in the platelet monitoring and treatment recommendations in the EAMS protocol (Supplementary Table 1). As per routine clinical practice, patients also received dietary and other lifestyle support at the lipid clinic appointments and were provided with a separate treatment protocol in a document titled "Information for Patients" prior to commencing treatment. All patients were already established on a low-fat diet, and dietary guidance and support was continued through the EAMS. After 6 months, a re-evaluation of therapy was recommended. In patients weighing ≥70

kg, the dose could be increased to a maximum of 285 mg once weekly, depending on TG level, goal of therapy, and platelet count (Supplementary Table 1). Patients were instructed to give each injection on the same day of the week as prior doses. Missed doses were to be administered as soon as possible unless the next scheduled dose was within 48 h, in which circumstance the missed dose was skipped and treatment resumed with the next regularly scheduled injection.

Prior to initiation of volanesorsen treatment, at least two separate platelet count measurements were performed. After commencing treatment, platelet levels were monitored every 2 weeks and results incorporated into the drug ordering system to ensure compliance with monitoring requirements and to allow receipt of additional drug supply. A 2-week dose pause was recommended in the event of a platelet count between $50 \times 10^9$/L and $100 \times 10^9$/L, and treatment was to be discontinued for a platelet count $<50 \times 10^9$/L (Supplementary Table 1). All adverse events (AEs), regardless of treatment association, were to be reported through a separate pharmacovigilance system.

Participants were male and female patients aged ≥18 years with genetically confirmed FCS who received treatment with volanesorsen in the EAMS and who provided written informed consent to participate in the study, including patients naive to volanesorsen treatment (treatment naive) as well as patients who previously received volanesorsen in the phase 3 APPROACH and/or APPROACH open-label extension (APPROACH-OLE) studies of volanesorsen (prior exposure).

### 2.2. Data collection

Data collected at EAMS baseline included year of birth, age at diagnosis, age at first volanesorsen injection, sex, ethnicity, confirmed FCS genotype, comorbidities, prior treatments for FCS, including surgery, and history of acute pancreatitis (prescriber defined). FCS-related treatment data (primarily TG and platelet levels), and clinician- and patient-reported outcomes were collected for the EAMS treatment period by review of each patient's clinical notes and medical records. All AEs reported for the EAMS treatment period were recorded in the pharmacovigilance system, from the date of the first dose of volanesorsen administration in the EAMS until 19 September 2020, the date the final participant exited the programme.

Hospitalisations with symptoms consistent with acute pancreatitis were captured for the 5-year period preceding any use of volanesorsen (retrospective period) and also for all time periods of volanesorsen treatment (prospective period). This allowed for an assessment of changes in incidence of pancreatitis before and during treatment with volanesorsen. For patients naive to volanesorsen prior to EAMS enrolment, retrospective pancreatitis data were collected for the 5-year period prior to the EAMS initiation period. For prior-exposure patients, equivalent data for the 5-year period prior to volanesorsen treatment initiation were already available from the APPROACH/APPROACH-OLE studies. The prospective period comprised the total time that participants were treated with volanesorsen, including EAMS participation as well as involvement in the APPROACH or APPROACH-OLE studies for the prior-exposure patients (Fig. 1). For the prior-exposure group, data captured during the APPROACH or APPROACH-OLE studies were also used to assess changes in key efficacy and safety parameters (TG levels, platelet counts) associated with treatment across the APPROACH/APPROACH-OLE studies and the EAMS in the current study.

### 2.3. Statistical analysis

All participants who received at least one dose of volanesorsen in the EAMS were included in the analyses. Data were analysed for the cohort overall and also according to the volanesorsen-naive and prior-exposure groups. "EAMS baseline" was defined as the average of the Day 1 assessment and the last measurement prior to Day 1 in EAMS. For the prior exposure group, "Pre-treatment baseline" was also captured,
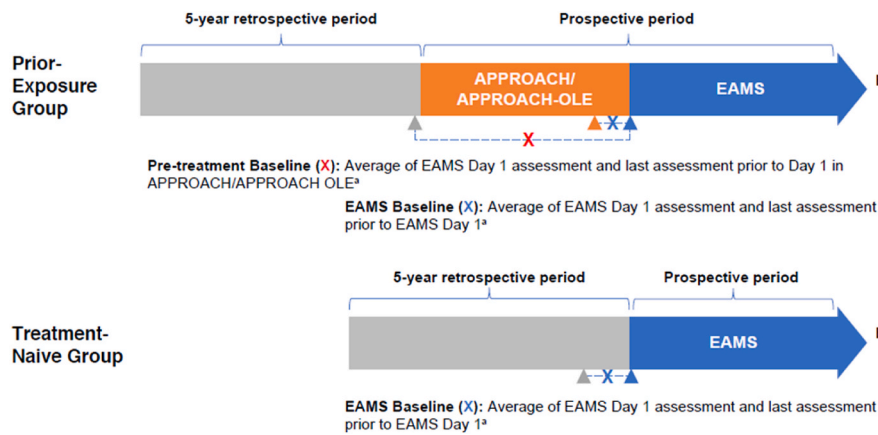
**Fig. 1.** Study design and data collection time periods. For the prior exposure group, the pre-EAMS initiation period includes data captured from participation in the APPROACH or APPROACH-OLE study ("Index Study"). For the treatment-naive group, the pre-EAMS initiation period is the 5-year period before EAMS Dose 1. EAMS Dose 1 is the date of the first dose of volanesorsen received via EAMS. The EAMS treatment period is the period from EAMS Dose 1 until the patient's exit date from the programme. Index study, APPROACH or APPROACH-OLE. [a]If one of the two measurements was missing, then the other measurement was assigned as the baseline value. If both were missing, then the baseline was set as missing. EAMS, Early Access to Medicines Scheme; OLE, open-label extension.

**Table 1**
Participant demographics and disease characteristics.

| Characteristic | Volanesorsen Naive (N = 12) | Prior Exposure (N = 10) |
|---|---|---|
| **Age at first injection (years)** | | |
| Median (min, max) | 44.0 (18.0, 68.0) | 43.5 (26.0, 66.0) |
| **Sex, n (%)** | | |
| Female | 7 (58.3) | 7 (70.0) |
| Male | 5 (41.7) | 3 (30.0) |
| **Race, n (%)** | | |
| Asian/South Asian | 6 (50.0) | 8 (80.0) |
| White | 6 (50.0) | 2 (20.0) |
| **Age at FCS diagnosis (years)** | | |
| Median (min, max) | 13.5 (0.5, 40.0) | 16.5 (0.4, 50.0) |
| **Genotype, n (%)** | | |
| LPL – homozygous | 6 (50.0) | 5 (50.0) |
| LPL – compound heterozygous | 2 (16.7) | 1 (10.0) |
| LPL/LMF1 – double heterozygous | 0 | 1 (10.0) |
| LMF1 – homozygous | 1 (8.3) | 0 |
| APOA5 – compound heterozygous | 2 (16.7) | 1 (10.0) |
| APOA5/GPIHBP1 – double heterozygous | 0 | 1 (10.0) |
| GPIHBP1 – homozygous | 0 | 1 (10.0) |
| Unspecified gene – homozygous | 1 (8.3) | 0 |
| **Hospitalizations consistent with acute pancreatitis in 5 years prior to treatment, n (%)** | | |
| Yes | 5 (41.7) | 5 (50.0) |
| No | 7 (58.3) | 5 (50.0) |
| **Number of hospitalizations consistent with acute pancreatitis in 5 years prior to treatment** | | |
| n (min, max) | 19 (0, 10) | 21 (0, 11) |
| **EAMS baseline triglycerides[a] (mmol/L)** | | |
| Median (min, max) | 26.4 (9.5, 57.8) | 18.3 (5.8, 35.4) |
| **Pre-treatment baseline triglycerides[a] (mmol/L)** | | |
| Median (min, max) | NA | 28.0 (3.9, 49.6) |
| **EAMS baseline platelet count[b] ($10^9$/L)** | | |
| Median (min, max) | 192.5 (157.5, 290.0) | 158.0 (120.0, 301.5) |
| **Pre-treatment platelet count[b] ($10^9$/L)** | | |
| Median (min, max) | NA | 238.5 (195.6, 340.7) |

APOA5, apolipoprotein A5; EAMS, Early Access to Medicines Scheme; FCS, familial chylomicronaemia syndrome; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; LMF1, lipase maturation factor 1; LPL, lipoprotein lipase; max, maximum; min, minimum; NA, not applicable.

[a] Baseline was defined as the average of Day 1 assessment and the last measurement prior to Day 1 assessment. If one of the two measurements was missing, then the other measurement was assigned as the baseline value. If both were missing, then the baseline was set as missing.

[b] Baseline was defined as the average of all pre-dose values for platelet count.

defined as the average of the Day 1 assessment and the last measurement prior to Day 1 in APPROACH or APPROACH-OLE (Fig. 1). If one of the two measurements was missing, then the other measurement was assigned as the baseline value.

The data summary included standard deviation, standard error of the mean, range (minimum, maximum), and 95% confidence intervals for the means. Where applicable, data are presented as median values with the range due to nonparametric distribution. Percent change and absolute change in TG levels over time were summarised using descriptive statistics, including averaged values. The proportion of patients with nadir platelet counts after the first volanesorsen dose in EAMS was summarised. The rate of acute pancreatitis events per month was calculated as the total number of events recorded in all patients during the relevant treatment period divided by the total number of completed months of treatment exposure in all patients. The annual rate was calculated by multiplying the monthly rate by 12. Treatment duration in days and months and proportion of patients with dose pauses were summarised using descriptive statistics. Date of first injection, participation in EAMS (in weeks), numbers of actual and missed doses, and percent dose administered were manually calculated and summarised. Demographics and baseline characteristics, as well as changes in TG and platelet levels, were summarised for two subgroups: patients with and

those without a history of hospitalisation consistent with pancreatitis on commencing treatment, and patients with a nadir platelet count $<100 \times 10^9$/L and those with a count $\geq 100 \times 10^9$/L during treatment.

### 2.4. Study oversight

The study protocol was reviewed and approved by the Health Research Authority in the United Kingdom, and by the Research Ethics Committee at each participating National Health Services Trust. The study complied with all applicable laws, regulations, and guidance regarding patient protection including privacy, and was consistent with the ethical principles of the Declaration of Helsinki and the requirements of the European Union General Data Protection Regulation.

## 3. Results

### 3.1. Participant disposition and demographics

A total of 22 participants treated with volanesorsen as part of the EAMS were included in this study. Of these, 12 were volanesorsen naive and 10 were previously treated with volanesorsen in the APPROACH and/or APPROACH-OLE trials. Of the 10 APPROACH trial participants, eight were transferred directly from APPROACH-OLE into the EAMS with no gap in treatment.

A summary of demographic and baseline characteristics is presented in Table 1. No notable differences were observed between the treatment-naive and previously treated patients. Overall, 14 (64%) patients were female and eight (36%) were male with a median age of 44 years (range, 18–68 years) at date of first volanesorsen injection in EAMS. Patients were of either South Asian (n = 14, 64%) or White (n = 8, 36%) ethnicity (Table 1), and 11 (50%) patients were homozygous for the LPL gene (Supplementary Table 2). Patients were diagnosed at a median age of 15 years, and 10 (45%) patients had experienced at least one prior hospitalisation consistent with acute pancreatitis in the 5 years before commencing volanesorsen treatment. Most patients (n = 19) had a

medical history of pancreatitis and all patients reported previous treatment with fibrates and low-fat diet. A total of 8 patients had diabetes mellitus either secondary to exocrine or endocrine pancreatic insufficiency or as a consequence of pancreatectomy. The majority of concomitant medications taken were related to drugs for high cholesterol and diabetes. No notable differences with regard to baseline characteristics were generally seen between patients who were or were not hospitalised due to an event consistent with acute pancreatitis, or between patients with a nadir platelet count $<100 \times 10^9$/L or $\geq 100 \times 10^9$/L (Supplementary Table 3).

### 3.2. Extent of drug exposure

In the treatment-naive group, the median time from the first volanesorsen dose to date of exit from the EAMS was 12.3 months (range, 6–22 months). In the prior-exposure group, exposure to volanesorsen was longer, as expected, with a median time of 35.5 months (range, 26–51 months).

As allowed per protocol, one patient was switched to weekly dosing from Week 45 to Week 52 but reverted to the standard every-2-week dosing frequency thereafter based on platelet count. Overall, treatment compliance was good, with 76% of all scheduled doses administered among the 22 patients in the programme (Supplementary Table 4). Of the 746 potential doses, 182 were not administered as scheduled for the following reasons: unspecified (92 missed doses); protocol-mandated dose pause (29 missed doses); AEs (20 missed doses); holiday/patient out of the country (20 missed doses); patients awaiting start of commercial supply (nine missed doses); pharmacy mistakenly disposed of medication (five missed doses); patient had COVID-19 infection (four missed doses); and voluntary dose pause, other illness, and lost blood results (one missed dose each). Two treatment-naive patients had particularly poor treatment compliance, with only 27% and 23% of their scheduled doses administered in the EAMS, respectively. Both patients failed to attend their lipid clinic appointments for long periods of time and were therefore unable to access platelet

**Table 2**
Averaged median, absolute change, and percent change in triglyceride levels (mmol/L) from baseline over time.

| Visit[a] | Volanesorsen Naive (N = 12) | | | | Prior Exposure (N = 10) | | | |
|---|---|---|---|---|---|---|---|---|
| | n | Median (min, max) | Mean Change From Baseline (min, max) | Mean Percent Change From Baseline (min, max) | n | Median (min, max) | Mean Change From Baseline (min, max) | Mean Percent Change From Baseline (min, max) |
| **Baseline** | 12 | 25.30 (9.46, 57.8) | NA | NA | 10 | 28.0 (3.9, 49.6) | NA | NA |
| Month 3 | 9 | 12.4 (2.6, 31.4) | −10.6 (−34.6, 9.0) | −52.0 (−92.9, 90.0) | 9 | 16.8 (6.8, 26.6) | −17.8 (−32.0, 11.4) | −51.3 (−80.4, 291.5) |
| Month 6 | 12 | 12.0 (2.8, 58.7) | −11.7 (−38.6, 47.8) | −55.2 (−92.5, 440.1) | 9 | 18.8 (10.9, 24.7) | −5.5 (−26.9, 7.0) | −24.8 (−64.6, 178.0) |
| Month 9 | 6 | 8.0 (6.1, 21.1) | −15.8, (−31.1, −8.8) | −52.5 (−83.5, −46.0) | 7 | 19.0 (2.4, 30.3) | −3.3 (−28.7, 0.4) | −28.8 (−81.4, 1.6) |
| Month 12 | 5 | 11.1 (8.0, 20.8) | −9.3 (−18.3, 9.4) | −46.8 (−63.7, 94.0) | 6 | 26.1 (16.1, 35.3) | −2.9 (−26.8, 4.0) | −9.7 (−54.1, 16.9) |
| Month 15 | 3 | 11.8 (10.9, 34.3) | −12.7 (−17.5, −4.8) | −51.8 (−61.7, −12.3) | 7 | 20.4 (13.7, 39.7) | −8.9 (−27.1, −0.1) | −37.6 (−57.5, −0.2) |
| Month 18 | 1 | 31.2 | −7.8 | −20.1 | 4 | 21.9 (18.0, 28.8) | −9.8 (−28.8, 0.7) | −28.4 (−58.2, 3.3) |
| Month 21 | 0 | NA | NA | NA | 2 | 18.7 (17.6, 19.9) | −4.3 (−6.2, −2.5) | −18.6 (−26.2, −10.9) |
| Month 24 | 0 | NA | NA | NA | 1 | 18.0 | −5.7 | −24.1 |
| Month 27 | 0 | NA | NA | NA | 0 | NA | NA | NA |

Max, maximum; min, minimum; NA, not applicable.

For the treatment-naive group, baseline was defined as the average of Day 1 assessment and the last measurement prior to Day 1 assessment in the EAMS. For the prior-exposure group, baseline was defined as the average of Day 1 assessment and the last measurement before exposure in APPROACH or APPROACH-OLE. If one of the two measurements was missing, then the other measurement was assigned as the baseline value. If both were missing, then the baseline was set as missing. Month 3 was defined as 85 days post-baseline ±30 days. Month 6 was defined as 176 days post-baseline ±30 days. Month 9 was defined as 267 days post-baseline ±30 days. Month 12 was defined as 358 days post-baseline ±30 days. Months 15, 18, 21, 24, and 27 were defined as 449, 540, 631, 722, and 813 days post-baseline ±30 days, respectively.
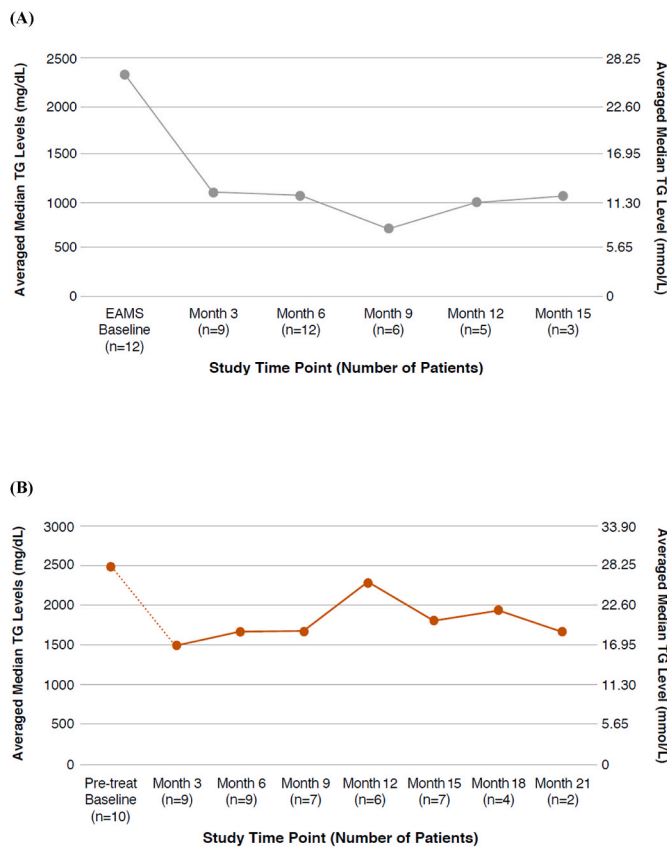
**(A)**



**(B)**



**Fig. 2.** Averaged median triglyceride levels during the EAMS treatment period. (A) Volanesorsen-naive group. (B) Prior-exposure group. For the treatment-naive group, baseline was defined as the average of Day 1 assessment and the last measurement prior to Day 1 assessment in EAMS ('EAMS baseline'). For the prior exposure group, baseline was defined as the average of Day 1 assessment and the last measurement before exposure in APPROACH or APPROACH-OLE ("Pre-treatment Baseline"); thus, the dotted line does not reflect a 3-month period. If one of the two measurements was missing, then the other measurement was assigned as the baseline value. If both were missing, then the baseline was set as missing. Month 3 was defined as 85 days post-baseline ±30 days. Month 6 was defined as 176 days post-baseline ±30 days. Month 9 was defined as 267 days post-baseline ±30 days. Month 12 was defined as 358 days post-baseline ±30 days. Months 15, 18, 21, 24, and 27 were defined as 449, 540, 631, 722, and 813 days post-baseline ±30 days, respectively. The time points at which these data were captured for each patient varied and was dependent on the frequency of attendance at the outpatient clinic; therefore, individual patients may vary from time point to time point, depending on availability of individual data. EAMS, Early Access to Medicines Scheme; Pre-treat, pre-treatment; TG, triglyceride.

monitoring and consequently resupply their medication per the terms of the EAMS. Together, these two patients accounted for 42% of the doses missed for unspecified reasons (39 of 92 doses).

### 3.3. TG levels

Table 2 presents averaged percentage and absolute changes in TG levels from baseline to various time points during the EAMS treatment period. Averaged median TG values at each time point are presented in Fig. 2A (treatment-naive group) and Fig. 2B (prior-exposure group).

In the treatment-naive group, the median baseline TG level was 26.4 mmol/L (2339 mg/dL) in the EAMS. At Month 3, a median 52% reduction in TG levels from baseline was observed, which corresponded to an averaged median TG level of 12.4 mmol/L (1094 mg/dL). Volanesorsen-naive patients continued to show a reduction from baseline in TG levels from Month 6 to Month 15 (last time point with data
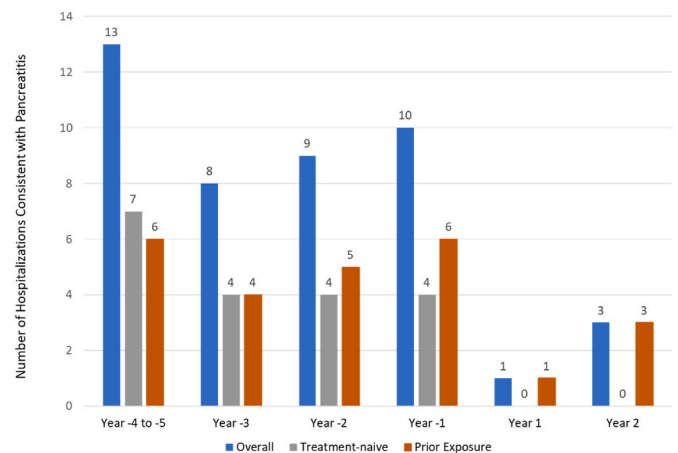


**Fig. 3.** Number of retrospective[a] and prospective[b] hospitalisations consistent with pancreatitis across all patients in EAMS.
[a]The retrospective period comprised a 5-year period prior to treatment in APPROACH, APPROACH-OLE, or EAMS for all 22 patients, plus the 'treatment gap' period for two patients who discontinued the index study early and initiated treatment in EAMS (14 and 28 months). The total length was calculated as follows: (22 patients x 5 years × 12 months) + 14 months +28 months = 1362 months. [b]The prospective period comprised the time on treatment in APPROACH, APPROACH-OLE, and EAMS (to the date of individual exit onto commercial supply) for all 22 patients. The total length was calculated as 528 months. EAMS, Early Access to Medicines Scheme.

from more than one patient), with averaged median TG values ranging from 8.0 to 12.0 mmol/L (709–1059 mg/dL), reflecting reductions of 47%–55%.

In the prior-exposure group, the median pre-treatment baseline TG level was 28.0 mmol/L (2478 mg/dL). Triglyceride levels continued to decrease from those achieved in the APPROACH or APPROACH-OLE study with continued treatment of volanesorsen in the EAMS. Averaged median TG levels decreased to 16.7 mmol/L (1482 mg/dL) at Month 3 in the EAMS, corresponding to a 51% reduction from baseline in TG levels. From Month 6 to Month 21 (last time point with data from more than one patient), there was a sustained reduction in TG levels among patients in the prior-exposure group, with averaged median TG values ranging from 18.7 to 26.1 mmol/L (1657–2308 mg/dL), or reductions from baseline of 9.7%–38%. Too few data points allowed further meaningful subgroup interpretation of the change in TG levels by history of hospitalisation consistent with pancreatitis or by nadir platelet level.

### 3.4. Pancreatitis events

Across all 22 patients, the duration of the retrospective period was approximately 1362 months. A total of 10 patients (five volanesorsen naive and five previously treated) were hospitalised with symptoms consistent with pancreatitis in the 5-year retrospective period (Fig. 3, details are presented in Supplementary Table 5). Overall, a total of 40 hospitalisations consistent with acute pancreatitis were reported during the 5-year retrospective review, primarily due to abdominal pain and pancreatitis. Across all 22 patients, the collective duration of exposure to volanesorsen during the prospective period was 528 months. During the APPROACH-OLE study, three patients were hospitalised due to pancreatitis (n = 1), nausea and abdominal pain (n = 1), and chronic pancreatitis (n = 1). Of these four events, only two were adjudicated as pancreatitis. During the EAMS treatment period, one previously treated patient reported symptoms of heartburn, central abdominal pain, and abdominal bloating similar to those experienced previously when suffering from pancreatitis. The patient was not hospitalised, and the event was recorded as "possible onset of pancreatitis." None of the
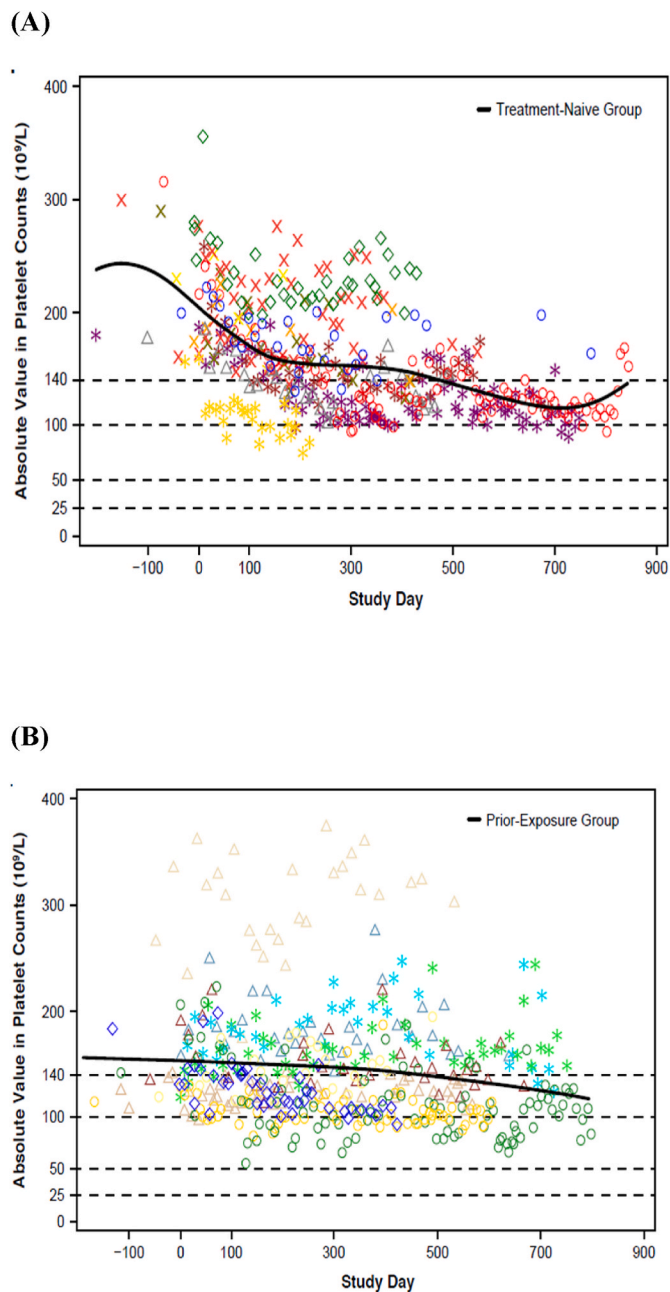
## (A)



## (B)



**Fig. 4.** Absolute platelet count values over time during the EAMS treatment period.
(A) Volanesorsen-naive group. (B) Prior-exposure group. All platelet counts were included regardless of whether the participant was on- or off-treatment, or the measurement was scheduled or unscheduled. Data lines represent dose groups and symbols represent individual participant data. EAMS, Early Access to Medicines Scheme.

treatment-naive patients experienced any symptoms consistent with pancreatitis during the EAMS treatment period. A comparison of the number of hospitalisations consistent with pancreatitis in the retrospective and prospective periods highlighted a change in incidence from an average of one event every 2.8 years to one event every 11.0 years (74% reduction).

### 3.5. Platelet counts

Absolute platelet counts during the EAMS treatment period are presented in Fig. 4A (treatment-naive group) and Fig. 4B (prior exposure

group). Changes in absolute platelet count during the EAMS treatment period are shown in Supplementary Fig. 1. In the treatment-naive group, the absolute platelet count fell by an average of approximately $50 \times 10^9$/L over the first 12 months of treatment and was broadly stable thereafter. In the prior-exposure group, the change in platelet count was broadly stable over the EAMS treatment period, having fallen by approximately $100 \times 10^9$/L following treatment with volanesorsen in the preceding APPROACH/APPROACH-OLE studies. The incidence of patients with nadir platelet count occurrence after the first volanesorsen dose in the EAMS is presented in Table 3. Overall, no patient had a platelet count $<50 \times 10^9$/L during the EAMS treatment period.

### 3.6. Safety

A total of 219 AEs of any grade were reported during the volanesorsen EAMS period (Table 4). The most commonly reported AEs were those classified as general disorders and administration site conditions, including injection site erythema (24 events) and injection site reactions (24 events), injection site pain (15 events), injection site pruritus and swelling (13 events each), injection site bruising (11 events), injection site discolouration (nine events), and injection site warmth (six events). Platelet count decreases were also common, with 18 events reported during the EAMS period. Overall, the majority of AEs were mild or moderate in severity (155/219, 71%) and nonserious (210/219, 96%). Nine of 219 events were considered severe, including one event each of pancreatitis, fatigue, injection site induration, injection site mass, injection site reaction, injection site swelling, injection site vesicles, injection site warmth, and lethargy.

A total of 24 bleeding events were reported in 10 patients in EAMS, including six events of thrombocytopenia (defined as platelet count $<140 \times 10^9$/mL) in four patients and 18 events of platelet count decrease in eight patients, all of which were considered nonserious. Of the 10 patients, two reported both thrombocytopenia events and platelet count decreases. There were no serious bleeding events that were associated with death or life threatening or resulted in hospitalisation.

A total of nine serious adverse events (SAEs) were reported in four patients in the volanesorsen EAMS: one treatment-naive patient reported two events of metastases to lung and one event each breast cancer metastatic and breast cancer recurrent; one treatment-naive patient reported new-onset coeliac disease; one treatment-naive patient reported one event each of syncope, dizziness, and hypotension; and one previously treated patient reported newly diagnosed diabetes mellitus. None of these events was assessed as related to study treatment. A total of three (14%) patients were discontinued from the EAMS programme, all due to AEs: one treatment-naive patient discontinued due to an SAE of metastatic breast cancer; one treatment-naive patient discontinued due to an SAE of coeliac disease; and one previously treated patient discontinued due to decreased weight. Following switch to a commercial supply of volanesorsen prior to the date the final study patient exited the volanesorsen EAMS, four additional patients withdrew or discontinued from treatment with volanesorsen: one treatment-naive patient discontinued due to SAEs of syncope, dizziness, and hypotension as well as other nonserious AEs (fatigue, flu-like symptoms, and injection site reactions), one previously treated patient voluntarily withdrew (wanting to become pregnant), and two treatment-naive patients were withdrawn due to failure to adhere to the homecare platelet monitoring service.

## 4. Discussion

This study (VOL4002) was undertaken to describe the efficacy and safety of volanesorsen in patients with genetically confirmed FCS treated in the UK EAMS. This included 10 patients who had commenced treatment in the APPROACH and/or APPROACH-OLE phase 3 clinical studies before transitioning into the EAMS, and 12 patients who were previously naive to volanesorsen treatment and commenced therapy in the EAMS. As such, the study allowed for a longitudinal assessment of treatment to

**Table 3**
Incidence of patients with nadir platelet count after first volanesorsen dose in the EAMS.

| Platelet Count | Volanesorsen Naive (N = 12) | Prior Exposure (N = 10) |
|---|---|---|
| Any 2 occurrences of platelet count <140,000/mm$^3$ or any single occurrence of platelet count <100,000/mm$^3$ | 7 (58.3) | 8 (80.0) |
| 100,000 to <140,000/mm$^3$ | 4 (33.3) | 4 (40.0) |
| 75,000 to <100,000/mm$^3$ | 3 (25.0) | 3 (30.0) |
| 50,000 to <75,000/mm$^3$ | 1 (8.3) | 1 (10.0) |
| 25,000 to <50,000/mm$^3$ | 0 | 0 |
| 0 to <25,000/mm$^3$ | 0 | 0 |

Data shown represent number (%) of patients.
EAMS, Early Access to Medicines Scheme.

**Table 4**
Medical history, concomitant medications, and adverse events by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term.

| Medical History | Number of Patients |
|---|---|
| Diabetes | 8 |
| Chronic pancreatitis | 5 |
| Prior history of ASCVD event | 0 |
| **Concomitant Medications** | **Number of Patients** |
| Statins | 10 |
| Fibrates | 12 |
| Omega-3 fatty acids | 7 |
| Orlistat | 3 |
| Nicotinic acid | 4 |
| **System Organ Class Preferred Term** | **Total Number of Events** |
| Any adverse event | 219 |
| **General disorders and administration site conditions** | **138** |
| Injection site erythema | 24 |
| Injection site reaction | 24 |
| Injection site pain | 15 |
| Injection site pruritus | 13 |
| Injection site swelling | 13 |
| Injection site bruising | 11 |
| Injection site discolouration | 9 |
| Injection site warmth | 6 |
| Fatigue | 5 |
| **Investigations** | **21** |
| Platelet count decreased | 18 |
| **Blood and lymphatic system disorders** | **7** |
| Thrombocytopenia[a] | 6 |

ASCVD, atherosclerotic cardiovascular disease.
[a] Defined as platelet count <140 × 10$^9$/L.

a maximum of 51 months, with a significant proportion of the treatment reflecting "real-world conditions" within the EAMS. Both of these are distinguishing features from the initial phase 3 studies upon which the conditional marketing authorisation for volanesorsen in the European Union was based (APPROACH and COMPASS) [11]. In the patients commencing treatment in the EAMS (treatment-naive group), treatment with volanesorsen 285 mg once every 2 weeks resulted in a median 52% reduction in TG levels at 3 months, equating to a reduction of 10.6 mmol/L. This reduction in TG levels was maintained throughout the EAMS treatment period, with averaged median TG reductions ranging from 47% to 55%. In the patients who commenced treatment with volanesorsen in the APPROACH or APPROACH-OLE studies (285 mg once every 1 week) prior to treatment in the EAMS (285 mg once every 2 weeks), a similar reduction in TGs was also observed at 3 months, namely, a 51% (17.8 mmol/L) reduction from the pre-treatment baseline. This reduction in TG levels was also maintained throughout the remainder of the EAMS treatment period, with averaged median TG reductions ranging from 10% to 38%. Whilst this reduction in TGs is lower than that observed in the APPROACH phase 3 study, it should be noted that the dose employed within the EAMS (prior to the awarding of the marketing authorisation) was half the recommended licenced dose for the first 3 months of treatment. Moreover, the lower range of averaged median reduction in TG observed in the prior treatment group

compared with that observed in the treatment-naive group could be due to the former group transitioning from weekly dosing in APPROACH and APPROACH-OLE to biweekly dosing in EAMS, thus experiencing a dose reduction. Despite this, no patients were hospitalised with symptoms consistent with pancreatitis during the EAMS treatment period, which represents a 74% reduction in the incidence of pancreatitis compared with the 5-years prior to commencing volanesorsen treatment.

In the APPROACH studies, thrombocytopenia was the most significant volanesorsen-related AE [12]. During the EAMS treatment period, the platelet count did not drop below the threshold of $<50 \times 10^9$/L in any participant, and platelet count drops to below $100 \times 10^9$/L recovered after temporarily withholding volanesorsen treatment. This demonstrated that platelet count monitoring in association with dose pausing is a successful strategy to avoid severe thrombocytopenia. However, the platelet monitoring and platelet reductions are acknowledged to be an issue, resulting in missed doses and hence sub-optimal drug exposure. Younger patients in particular find the frequent monitoring a burden, more so than the injection itself. A potential benefit of frequent platelet monitoring is the ability to also monitor fasting TG levels at the same time. This may highlight variability in TG levels and encourage adherence to the very low-fat diet, the main factor in determining the patient's TG levels. Not unexpectedly, the absolute platelet count showed marked inter- and intra-participant variability during the EAMS, as has been previously reported in both untreated and volanesorsen-treated patients with FCS, suggesting that the disease is associated with fluctuations in platelet count over time, possibly as a consequence of the hepatosplenomegaly inherent to the condition [3, 13]. Consistent with the APPROACH studies, injection site reactions were the most commonly reported AEs in the EAMS treatment period. (General disorders and administration site conditions accounted for more than half [63%] of the adverse events reported.) Overall, the majority of AEs were mild or moderate in severity and nonserious. A total of nine SAEs were reported in four patients in the volanesorsen EAMS; none of these events was assessed as related to study treatment. No new safety signals were associated with the increased duration of exposure reflected in these data.

The experience of the patients treated with volanesorsen within the EAMS study was mainly very positive. Some patients who experienced repeated episodes of acute pancreatitis and multiple hospital admissions reported that treatment with volanesorsen improved disease and symptom burden and reduced the number of episodes of acute pancreatitis and hospital admissions. However, a number of other patients have discontinued treatment (since the study finished) due to side effects, mostly low platelet counts but also acute or chronic immune reactions. These patients have been ambivalent about restarting treatment where it was offered, preferring instead to adhere to an ultra low-fat diet allied with medium-chain triglyceride (MCT) oil. Overall, most patients in the study have experienced symptom improvement and are keen to continue on volanesorsen treatment.

During the EAMS, clinical efficacy data including TG levels and hospitalizations with pancreatitis were recorded as part of routine care with data retrospectively collected for the current study. Because routine care was being accessed in a variety of settings including primary care and local hospitals, and not necessarily from the healthcare

provider prescribing volanesorsen via the EAMS, the data may be incomplete or, for some participants, limited to only a few data points. This is a limitation of the current study, although it does also reflect the use of volanesorsen in real-world practice in the United Kingdom. Despite these limitations, this study provides further support for the use of volanesorsen as adjunctive treatment to a very low-fat diet to reduce the incidence of acute pancreatitis in patients with FCS, thereby fulfilling a prior unmet clinical need.

### Financial support

### Data sharing statement

Data that underline the results reported in this article and the respective individual participant data will not be shared.

### Author contributions

AJ was the VOL4002 study PI, with responsibility for submitting the study protocol to the United Kingdom (UK) Health Research Authority (HRA), overall conduct of the study and verification of the accuracy of the study data and content of the clinical study report. AJ, KP, ASW, RR, MM, CD, AO-F, HS, FJ, IMD, PD and PH were the treating Healthcare Professionals with responsibility for submitting the VOL4002 study protocol to the Research Ethics Committee at their participating National Health Service (NHS) Hospital Trust, management of their patients within the EAMS per the terms of the EAMS Treatment protocol and/or the collection and submission of the study data for analysis. All authors had responsibility for the interpretation of the data, writing the manuscript and the decision to submit the paper for publication.

### Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:AJ has no conflicts of interest to declare.KP has no conflicts of interest to declare.ASW is a site investigator for clinical trials for Akcea, Amgen, Regeneron, and Sanofi.RR has no conflicts of interest to declare.MM has no conflicts of interest to declare. CD has no conflicts of interest to declare.AOF has no conflicts of interest to declare.HS has received research and education grants and honoraria from Akcea Therapeutics. FJ has no conflicts of interest to declare.IM has no conflicts of interest to declare.PD has received speaker fees and honoraria from Akcea Therapeutics for attendance at Advisory boards.PH has no conflicts of interest to declare.RJ was an employee of Akcea Therapeutics at the time the study was undertaken.

### Acknowledgments

### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2023.05.008.

### References

[1] D. Gaudet, E. Karwatowska-Prokopczuk, S.J. Baum, E. Hurh, J. Kingsbury, et al., Vupanorsen, an N-acetyl galactosamine-conjugated antisense drug to ANGPTL3 mRNA, lowers triglycerides and atherogenic lipoproteins in patients with diabetes, hepatic steatosis, and hypertriglyceridaemia, Eur. Heart J. 41 (2020) 3936–3945, https://doi.org/10.1093/eurheartj/ehaa689.

[2] M. Davidson, M. Stevenson, A. Hsieh, Z. Ahmad, J. Roeters van Lennep, et al., The burden of familial chylomicronemia syndrome: results from the global IN-FOCUS study, J Clin Lipidol 12 (2018) 898–907.e2, https://doi.org/10.1016/j.jacl.2018.04.009.

[3] R.A. Hegele, J. Borén, H.N. Ginsberg, M. Arca, M. Averna, et al., Rare dyslipidaemias, from phenotype to genotype to management: a European Atherosclerosis Society task force consensus statement, Lancet Diabetes Endocrinol. 8 (2020) 50–67, https://doi.org/10.1016/S2213-8587(19)30264-5.

[4] R.A. Hegele, A.J. Berberich, M.R. Ban, J. Wang, A. Digenio, et al., Clinical and biochemical features of different molecular etiologies of familial chylomicronemia, J Clin Lipidol 12 (2018) 920, https://doi.org/10.1016/j.jacl.2018.03.093, 7.e4.

[5] D.J. Blom, L. O'Dea, A. Digenio, V.J. Alexandeer, E. Karwatowska-Prokopczuk, et al., Characterizing familial chylomicronemia syndrome: baseline data of the APPROACH study, J Clin Lipidol 12 (2018) 1234, https://doi.org/10.1016/j.jacl.2018.05.013, 43.e5.

[6] Z. Ahmad, R. Halter, M. Stevenson, Building a better understanding of the burden of disease in familial chylomicronemia syndrome, Expet Rev. Clin. Pharmacol. 10 (2017) 1–3, https://doi.org/10.1080/17512433.2017.1251839.

[7] D. Davidson, C. Slota, M. Vera-Llonch, T.M. Brown, A. Hsieh, et al., Development of a novel PRO instrument for use in familial chylomicronemia syndrome, J Patient Rep Outcomes 5 (2021) 72, https://doi.org/10.1186/s41687-021-00347-5.

[8] O. Esan, A.S. Wierzbicki, Volanesorsen in the treatment of familial chylomicronemia syndrome or hypertriglyceridaemia: design, development and place in therapy, Drug Des. Dev. Ther. 14 (2020) 2623–2636, https://doi.org/10.2147/DDDT.S224771.

[9] D. Gaudet, D. Brisson, K. Tremblay, V.J. Alexander, W. Singleton, et al., Targeting APOC3 in the familial chylomicronemia syndrome, N. Engl. J. Med. 371 (2014) 2200–2206, https://doi.org/10.1056/NEJMoa1400284.

[10] D. Gaudet, V.J. Alexander, B.F. Baker, D. Brisson, K. Tremblay, et al., Antisense inhibition of apolipoprotein C-III in patients with hypertriglyceridemia, N. Engl. J. Med. 373 (2015) 438–447, https://doi.org/10.1056/NEJMoa1400283.

[11] J. Paik, Duggan S. Volanesorsen, First global approval, Drugs 79 (2019) 1349–1354, https://doi.org/10.1007/s40265-019-01168-z.

[12] J.L. Witztum, D. Gaudet, S.D. Freedman, V.J. Alexander, A. Digenio, et al., Volanesorsen and triglyceride levels in familial chylomicronemia syndrome, N. Engl. J. Med. 381 (2019) 531–542, https://doi.org/10.1056/NEJMoa1715944.

[13] D. Gaudet, A. Baass, K. Tremblay, D. Brisson, N. Laflamme, et al., Natural history (up to 15 years) of platelet count in 84 patients with familial hyperchylomicronemia due to lipoprotein lipase deficiency [abstract], J Clin Lipidol 11 (2017) 797–798.