

Volanesorsen in the Treatment of Familial Chylomicronemia Syndrome or Hypertriglyceridaemia: Design, Development and Place in Therapy

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Oluwayemisi Esan 
Anthony S Wierzbicki 

Department of Metabolic Medicine/
Chemical Pathology, Guy's & St Thomas'
Hospitals, London SE1 7EH, UK

Abstract: Severe hypertriglyceridaemia is associated with pancreatitis and chronic pancreatitis-induced diabetes. Familial chylomicronaemia syndrome (FCS) is a rare autosomal recessive disorder of lipid metabolism characterised by high levels of triglycerides (TGs) due to failure of chylomicron clearance. It causes repeated episodes of severe abdominal pain, fatigue and attacks of acute pancreatitis. There are few current options for its long-term management. The only universal long-term therapy is restriction of total dietary fat intake to <10-15% of daily calories (15 to 20g per day). Many patients have been treated with fibrates and statins with a variable response, but many remain susceptible to pancreatitis. Other genetic syndromes associated with hypertriglyceridaemia include familial partial lipodystrophy (FPLD). Targeting apolipoprotein C3 (apoC3) offers the ability to increase clearance of chylomicrons and other triglyceride-rich lipoproteins. Volanesorsen is an antisense oligonucleotide (ASO) inhibitor of apoC3, which reduces TG levels by 70–80% which has been shown also to reduce rates of pancreatitis and improve well-being in FCS and reduce TGs and improve insulin resistance in FPLD. It is now undergoing licensing and payer reviews. Further developments of antisense technology including small interfering RNA therapy to apoC3 as well as other approaches to modulating triglycerides are in development for this rare disorder.

Keywords: triglyceride, pancreatitis, familial chylomicronaemia syndrome, lipoprotein lipase, chylomicron, lipodystrophy, familial partial lipodystrophy, volanesorsen

Plain Language Summary

High levels of blood fats (triglycerides) are linked to higher rates of hospital admission for stomach (abdominal) aches and especially for inflammation of the pancreas (pancreatitis). In some rare people, high levels of triglycerides are caused by defects in the genes coding for enzymes that digest large fat particles (chylomicrons) in the bloodstream or by defects that mean that fats cannot be stored in fat tissue. These fat particles contain a protein (apoC3) that controls their rate of degradation. Volanesorsen is a member of a new class of drugs that stop proteins being made and specifically blocks the making of apoC3. In clinical studies, volanesorsen has been shown to reduce blood fat levels and to reduce the severity of abdominal pain and admissions for pancreatitis.

Correspondence: Anthony S Wierzbicki
Department of Chemical Pathology,
St. Thomas' Hospital, Westminster Bridge
Road, London SE1 7EH, UK
Tel +0207 188 1256
Fax +0207 188 7325
Email anthony.wierzbicki@kcl.ac.uk

Introduction

Hypertriglyceridaemia

Significant hypertriglyceridaemia occurs in 11% while severe hypertriglyceridaemia (Fredrickson type 5 or type 1) has an incidence of 1 in 1000.^{1,2} The differential diagnosis includes new uncontrolled diabetes, excess alcohol intake, and some drug therapies but many cases have a genetic component.² Most cases of moderate (200–1000mg/dl; \approx 2–10mmol/l) and severe hypertriglyceridaemia (>1000mg/dl; \approx 10mmol/L) are polygenic in origin.^{3,4} Extreme hypertriglyceridemia requiring emergency assessment is defined as >2000mg/dl (\approx 20mmol/l). Monogenic conditions causing severe hypertriglyceridaemia include familial chylomicronaemia syndrome (FCS) and familial partial lipodystrophy (FPL). Any form of hypertriglyceridaemia is associated with exponentially increasing risk for developing pancreatitis rather than coronary heart disease.² The risk of pancreatitis and CVD is significantly increased in subjects with non-fasting TG concentrations >443mg/dl (5mmol/L).⁵ An extreme TG group (>2000mg/dl; \approx 20mmol/L) has been suggested to have a 25-fold increase risk of pancreatitis⁶ though many cases seem to present at >3000mg/dl (35mmol/L).⁷

Clinical Features of Chylomicronaemia Syndrome

Familial chylomicronaemia syndrome (FCS) is a rare autosomal recessive disorder with an estimated prevalence of 1 in 1000,000.^{8,9} It may be more frequent as milder cases have not been genetically diagnosed.¹ FCS can present in childhood or early adulthood. The presence of pancreatitis, recurrent episodes of abdominal pain, lipemia retinalis (visible intraarterial hypertriglyceridemia) or eruptive xanthomata are often considered pathognomonic for a chylomicronaemia syndrome.¹⁰ A few cases that cause a phenocopy of FCS are caused by autoimmune reactions to components of the LPL pathway.^{11,12}

FCS has profound consequences having an increased risk of mortality and complications secondary to pancreatitis as shown in a series of 221 patients with triglyceride-induced pancreatitis¹³ and also on quality of life as documented in a study of 166 patients with FCS.¹⁴ The median age of FCS patients was 33 years with a median age at diagnosis of 9 years. Hospital admissions were frequent with 40% being admitted in the past year often involving stays on intensive care. Pancreatitis had occurred in 40% with a lifetime mean of 13 episodes per patient and 53% remained symptomatic

for abdominal pain despite being on a strict diet. Thus, having FCS has profound effects on employment status, emotional/mental well-being, and social relationship.^{14,15}

Lipid Biochemistry

Chylomicronaemia syndromes are caused by defects in the lipoprotein lipase (LPL) pathway for metabolism (catabolism) of triglyceride-rich lipoproteins (TGRL). LPL is required for the hydrolysis of triglycerides (TGs) in chylomicrons (CMs) and very-low-density lipoprotein (VLDL) particles. Chylomicrons contain a shortened form of apolipoprotein B (B₄₈) made specifically in gut enterocytes while liver-synthesised VLDL contains full-length apoB (apoB₁₀₀). Chylomicrons in contrast to VLDL particles seem to be pro-inflammatory in the general circulation.^{16,17} In patients with chylomicronaemia syndrome, the fasting plasma is turbid and if left undisturbed for several hours, CM float to the top and form a creamy supernatant layer.¹⁸ Fasting TG levels are almost invariably >1500 mg/dL (\approx 15mmol/L) and not infrequently rising as high as 10,000 mg/dL (\approx 100mmol/L) or more.⁴ Parallel but lesser elevations occur in cholesterol levels. While chylomicronaemia predominates, patients often have elevated plasma levels of CM remnants and some VLDL as well.¹⁹ Lipoprotein electrophoresis demonstrates a type 1 (CM) or type 5 (excess VLDL) pattern. Lipid ultracentrifugation is considered the optimal diagnostic method for chylomicronaemia and shows significant excess triglyceride in CM and/or VLDL density fractions but is not widely available. The simpler biochemical phenotype in the lipid profile is of a disproportionately raised triglyceride level compared to the apolipoprotein B₁₀₀ concentration, given the relative lack of VLDL, and is used as the basis of diagnostic algorithm.²⁰ This is caused by an excess of apolipoprotein B₄₈ containing CM particles as opposed to apoB₁₀₀ containing VLDL. Measurements used to be made of LPL activity, but these are difficult to perform and standardise so genetic diagnosis is now preferred.

Genetics of Familial Chylomicronaemia Syndrome

FCS is an inherited autosomal recessive disease caused by mutations in LPL (lipoprotein lipase) and in other genes encoding proteins required for LPL activity, such as apolipoprotein (apo) C2, apoA5, lipase maturation factor-1 (LMF-1) and glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1).³ The most common cause of FCS involves mutations in the LPL gene.²¹

Heterozygotes with LPL variants often have moderate elevations in plasma TG levels and increased risk for CHD.^{22,23} ApoC2 is a required cofactor for LPL activation.²⁴ ApoC2 deficiency results in functional lack of LPL activity and chylomicronaemia but with a less severe in phenotype than LPL mutations.²⁵ ApoA5 facilitates the association of VLDL and chylomicrons with LPL and promotes hydrolysis of the TGs.²⁶ GPIHBP1 is required for transport and tethering of LPL to the endothelial luminal surface and acts as an endothelial binding ligand for CMs.²⁷

Current Treatment of FCS

Treatment for FCS involves management of both acute exacerbations of chylomicronaemia as well as chronic management to reduce the probability of destabilisation.

Acute treatment for FCS involves fasting to reduce CM production and increase natural clearance plus management of any hyperglycaemia in addition to supportive treatment for any underlying pancreatitis.^{28,30} Lipoprotein removal through plasmapheresis removes triglyceride-rich lipoproteins (TGRLs) acutely and is preferred to apheresis.³¹ Clinical algorithms for acute management of TG-related pancreatitis are available.^{30,31}

The only universal current long-term therapy is restriction of total fat intake to less than 10–15% of daily calories (15 to 20g per day).³² This is challenging and found difficult by 90% of patients.¹⁴ It can also be ineffective in preventing chylomicronaemia and acute pancreatitis. Medium-chain triglycerides are also used in patients with FCS as these are not incorporated into CMs though are a substrate for energy metabolism.^{33,34} Some patients have been treated with fibrates,^{31,35} omega-3 fatty acids^{33,36} and statins³⁷ with reasonable clinical response³¹ but this approach is more typically useful in multifactorial chylomicronaemia syndrome (MCS).^{29,38,39} This data is consistent with lipoprotein kinetics studies. Though none have been performed in patients with FCS where LPL-related particle catabolism is significantly impaired, studies in patients with hypertriglyceridaemia (Fredrickson types 2B-5) show 20–30% reductions in apoB48 particle production rates with fibrates,⁴⁰ omega-3 fatty acids⁴¹ and statins⁴² as well as the expected effects on fractional catabolic rates. Anecdotal reports exist of the response of patients with FCS to splenectomy⁴³ or biliary-pancreatic diversion.⁴⁴

Familial Partial Lipodystrophy

Lipodystrophy syndromes are rare and can be genetic or acquired. They are characterised by variable body fat loss and associated metabolic complications, including insulin

resistance, dyslipidaemias especially hypertriglyceridaemia, hepatic steatosis and atherosclerotic cardiovascular disease (ASCVD).^{4,45} The four main types of lipodystrophy (excluding antiretroviral therapy-induced lipodystrophy in HIV-infected patient) are the genetic types congenital generalised lipodystrophy (CGL), and familial partial lipodystrophy (FPLD),⁴⁶ while acquired generalised lipodystrophy (AGL) and acquired partial lipodystrophy (APL) may have an autoimmune component and can be metabolically severe.⁴⁷ FPLD is caused by mutations in multiple genes including lamin and peroxisomal proliferator activator receptor-gamma (PPAR- γ) genes and is associated with moderate degrees of fat loss, extreme insulin resistance, type 2 diabetes and significant hypertriglyceridaemia in type 2 (Dunnigan) or type 1 (Kobberling) disease.^{4,48,49} Studies of apoC3 inhibition have only been proposed in FPL as both fibrates and thiazolidinediones have been used in the treatment of type 2 FPLD.⁴

Apolipoprotein C3 as a Drug Target

The clearance of TGRL is dependent on the activities of the LDL (apoB₁₀₀/E), VLDL-receptor, LDL related protein-1 (LRP1) and apoE type 2 receptors⁵⁰ and, possibly for CM in the gut, the SRB1 receptor.⁵¹ The binding of TGRL to these receptors is modulated by apoE and apoC with apoE increasing while apoC^{52,53} or apoC1 decreases clearance (Figure 1).

In patients with excess triglycerides more CM and VLDL particles seem to be secreted containing apoC3 and with less apoE.⁵⁴ ApoC3 may also directly regulate enterocyte metabolism of TGs.⁵⁵ Deficiency of apoC3 in man is associated with hypolipoproteinaemia including reductions in triglycerides and these effects can be mimicked by antibodies to apoC3.⁵⁶ Drugs such as fibrates,^{57,58} niacin^{59,60} and omega-3 fatty acids⁶⁰ reduce apoC3 levels but have their principal effect on VLDL (apoB₁₀₀) metabolism. Thus, reductions of apoC3 by these drugs may be secondary to VLDL turnover. ApoC3 may also directly inhibit LPL activity.⁶¹ Fibrates may also increase enterocyte apoA5 production.⁶² Other proteins promoting LPL activity such as LMF-1, GPIHBP-1 promote TGRL clearance while angiopoietin-like peptides (ANGPTL) retard TGRL clearance by inhibiting LPL activity.⁶³ Thus, extensive animal, human and interventional data exist that apoC3 is a good pharmaceutical target for intervention to lower triglycerides. The evidence for the effects of apoC3 in chylomicron metabolism are less strong than for VLDL but sufficient to suggest that intervention would be efficacious in patients lacking LPL pathway function.

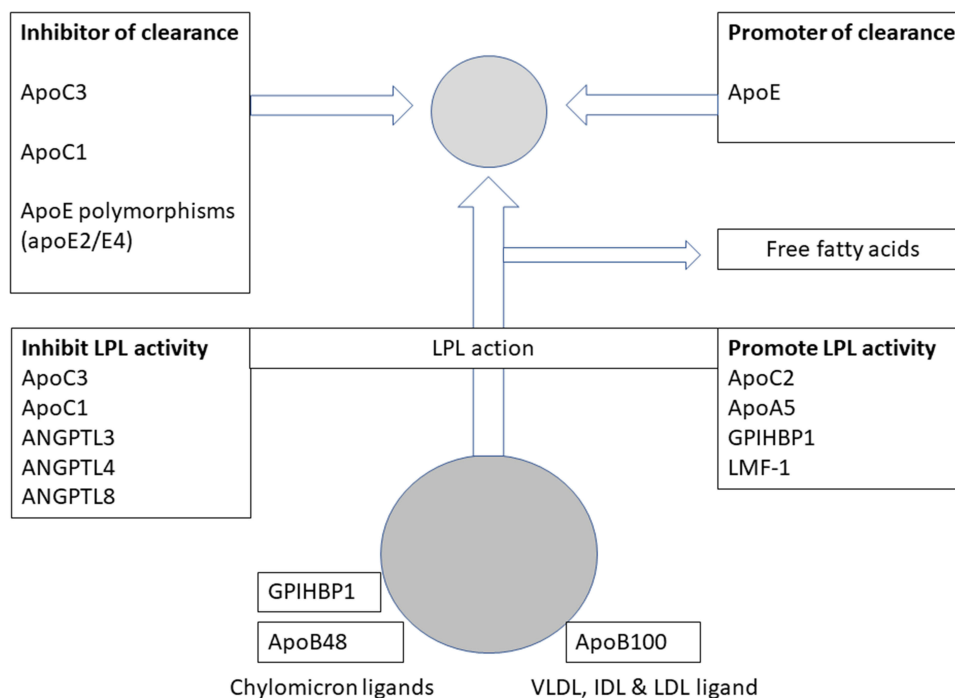


Figure 1 Apolipoproteins and other proteins influencing the clearance of chylomicrons or very-low-density lipoprotein particles and affecting the activity of lipoprotein lipase.

Abbreviations: ANGPTL, angiopoietin-like protein; Apo, apolipoprotein; CM, chylomicron; GPIHBP1, glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1; LMF-1, lipase maturation factor-1.

Chemistry and Pharmacodynamics

Volanesorsen (ISIS 304801; ISIS-ApoC-III Rx) is a second-generation 2'-O-methoxyethyl (2'-MOE) chimeric antisense therapeutic oligonucleotide (ASO).⁶⁴ It selectively binds within the 3' untranslated region (at base position 489–508) of apoC3 messenger ribonucleic acid (mRNA).⁶⁵ This binding prevents the translation of the apoC3 mRNA and allows ribonuclease H1-mediated mRNA degradation, thereby promoting triglyceride clearance and the lowering of plasma triglyceride levels through LPL-independent pathways. These pathways include apoC3 inhibiting hepatic receptor-mediated pathways mediated by the LDLR and LRP1.⁶⁵ Volanesorsen selectively reduced apoC3 mRNA in a concentration-dependent manner in human hepatoma cell line and primary human hepatocytes. As a result, administration of volanesorsen is associated with dose-dependent reductions in plasma apoC3 and a parallel reduction in triglycerides level.⁶⁵

Pharmacokinetics

Volanesorsen is administered subcutaneously. In a Phase 1 clinical study on healthy volunteers, volanesorsen exhibits dose-dependent pharmacokinetics over the dose range of 50–400mg with respect to peak concentrations (C_{max}) and the area

under the time-concentration curve 24h after dosing (AUC_{0-24hr}).^{65,66} Following subcutaneous injection across the 50–400mg dose range, peak plasma concentrations are typically reached in 2 to 4 hours and the absolute bioavailability of following a single subcutaneous administration is approximately 80% (most likely higher because an AUC of 0 to 24 hours was used and volanesorsen has a half-life of >2 weeks).⁶⁷

Volanesorsen was rapidly and widely distributed to tissues from plasma with short mean residence times 6.4–8.1hrs⁶⁵ and the plasma elimination half-life in the healthy volunteers receiving multiple doses of the drug ranged from 12 to 31 days with clearance primarily through urinary excretion of metabolites.⁶⁸ Proof of concept with volanesorsen in FCS was demonstrated in 3 patients with FCS, following a dose of 285 mg once weekly or fortnightly, the estimated geometric mean (coefficient of variation as percentage of geometric mean) steady-state C_{max} and AUC were similar while steady-state trough concentrations (C_{trough}) were higher with once weekly dosing.⁶⁹ The estimated steady-state volume of distribution in patients with FCS is 330L. It is highly bound to human plasma proteins (>98%) but the binding is concentration independent. It is not a substrate for cytochrome metabolism but is

metabolised in tissues by endonucleases to form shorter oligonucleotides that are then degraded by exonucleases.⁶⁸

Clinical Efficacy

Several clinical trials have documented the efficacy of volanesorsen in the treatment of FCS and elevated TGs.

Early Phase Clinical Trials

The phase 1 proof of concept first in human study (CS1) was conducted in 33 healthy subjects. Volanesorsen was administered on alternate days during the first week (Days 1, 3 and 5) and then once-weekly for the next 3 weeks (Days 8, 15 and 22). Treatment resulted in dose-dependent substantial reductions in apoC3 of 20%, 17%, 71%, and 78% on Day 29, 1 week after the last dose, at doses of 50, 100, 200, and 400 mg, respectively, which was associated with dose-dependent reductions in TGs of 20%, 25%, 43%, and 44%.⁶⁵

Changes in triglycerides correlated with change in apoC3 ($r=0.89$) and 2 out of 3 subjects showed suppression of apoC3 production at the 400mg dose.

In Phase 2, randomized, double-blind, placebo-controlled, dose-response study (CS2) volanesorsen was administered weekly subcutaneously for 13 weeks in 57 subjects with severe or uncontrolled hypertriglyceridemia (randomised 41:16) and 28 on fibrate therapy (randomised 20:8)⁷⁰ (Table 1). Recruitment was by TG levels 350–2000mg/dl (4–23mmol/L) in the untreated group and TG

250–2000mg/dL (3–23mmol/l) for those on fibrate-statin therapy.⁷⁰ Baseline triglyceride levels in the 2 cohorts were 581±291 mg/dL (6.6±3.3mmol/L) and 376±188 mg/dL (4.2±2.1 mmol/L). ApoC3 levels were reduced in a dose-proportional manner from 100–300mg compared to a rise on placebo (Table 2). These corresponded to 31–79% reductions in TG (least squares mean) compared to a 20% rise on placebo. Similarly, when volanesorsen was added to fibrate therapy apoC3 again decreased in a dose-proportional manner from 200 to 300mg, allied with concordant reductions of 52–65% were observed in triglycerides.⁷⁰

In a subgroup of the main phase 2 study, 3 patients with FCS and triglyceride levels ranging from 1406 to 2083 mg/dL (16–24 mmol/L) received volanesorsen for 13 weeks. Plasma apoC3 levels were reduced by 71–90% and TGs by 56–86% and all patients achieved a TG<500 mg/dL (5.7mmol/L).⁶⁹

Phase 3 Clinical Trials

Approach (CS6)

The CS6 (APPROACH) phase 3 study evaluated the efficacy and safety of volanesorsen in 66 adult patients with TG>750mg/dl (8.48mmol/L) with clinical FCS from 130 patients screened and forms the key evidence for volanesorsen (Table 2). In the randomised cohort, 41 patients were homozygous or compound heterozygotes for 25 different inactivating mutations in *LPL*, and 11 patients had biallelic mutations in accessory proteins or were double

Table 1 Response of apoC3 and Triglyceride Levels to Volanesorsen Therapy in Patients with Hypertriglyceridaemia (Study CS2)⁷⁰

	Placebo	100mg	200mg	300mg	Fibrate-Placebo	Fibrate and 200mg	Fibrate and 300mg
ApoC3 Baseline (mg/dL)	22±8	22±8	23±5	23±6	19±6	16±4	18± 6
ApoC3 Treated (mg/dl)	22± 11	12± 5	8 ±4	4 ±2	18±4	6±3	5± 2
Change (least- squares mean %)	4±8	-39±9	-64±8	-80±9	-2± 6	-61±6	-72± 5
Triglycerides baseline mg/dl Median & IQR	459 (356–582)	558 (351–825)	588 (464–717)	566 (355–702)	475 (253–602)	272(230–295)	271(241–459)
Triglycerides baseline (mmol/L) median & IQR	5.2 (4.02–6.58)	6.31 (3.97–9.33)	6.64 (5.24–8.10)	6.40 (4.01–7.93)	5.37 (2.86–6.80)	3.07(2.59–3.33)	3.06(2.72–5.19)
Triglycerides treated (mg/dl) Median & IQR	456 (343–640)	277 (226–394)	180 (157–262)	120 (115–185)	338 (290–394)	120(103–172)	116(91–191)
Triglycerides treated (mmol/L) Median & IQR	5.15 (3.86–7.23)	3.13 (2.55–4.45)	2.03 (1.30–2.96)	1.36 (1.30–2.09)	3.82 (3.28–4.45)	1.36(1.17–1.94)	1.31(1.03–2.16)
Change (least- squares mean %)	20±13	-31±15	-59±14	-71±15	-8±7	-52±7	-65±6

Table 2 Key Phase 3 Clinical Trials of Volanesorsen

Study/Study Population	Primary Objective	Study Design	Dose (mg)	Subjects	Parameters	Placebo Baseline mg/dl (mmol/L)	Placebo On-Treatment mg/dl (mmol/l)	Volanesorsen Baseline mg/dl (mmol/L)	Volanesorsen On-Treatment mg/dl (mmol/L)	Change (%)
ISIS304801-CS6 (APPROACH) ⁷² Patients with FCS	Efficacy Safety	Randomized, Double-Blind, Placebo Controlled,	300 mg Once weekly for 52 weeks	Volanesorsen: 33 Placebo: 33	TG CM-TG ApoB ₄₈ ApoB ₁₀₀ ApoC3	2152 ±1153 (24.3 ±13.0) 1785 ±1149 (20.2 ±13.0)	2367±1315 (26.7±14.9) 1991±1279 (22.5±14.5) 9.9±6.9 70.4±22.7 30.7±16.1	2267±1259 (25.6±14.4) 1913±1216 (21.6±13.7) 11.2±7.1 64.7±19.5 31.4±15.3	590±497 (6.7±5.6) 436±480 (4.93±5.4) 2.6±2.4 75.9±27.1 4.6±2.8	18 vs.- 77 29 vs -83 14 vs -76± 4 vs 20 6 vs -84
ISIS 304801-CS7 ^a (APPROACH OLE) ⁷⁶ Patients with FCS	Safety	Open-Label Study.	300 mg Once weekly for 52 weeks	Volanesorsen: 67 50 naive 14 CS6 continuing 3 CS16 continuing	Naïve TG CS6 TG CS16 TG	9.3±6.0 69.4±19.8 28.9±13.1		2317±1993 (26.1±22.5) 2641±1228 (29.8±13.9) 2288±1524 (25.9±17.2)	979±683 (11.1±7.7) 1248±927 (14.1±10.5) 1558±193 (17.6±2.2)	-47 -55 -39
ISIS 304801-CS16 ^b (COMPASS) ⁷⁶ Patients with Hypertriglyceridaemia	Efficacy Safety	Randomized, Double-Blind, Placebo Controlled,	300 mg Once weekly for 26 weeks ^c	Volanesorsen: 75 (5 FCS) Placebo: 38 (2 FCS)	TG	1414 ±1253 (16.0 ±14.2)	1406±1409 (15.9±15.9)	1183±759 (13.4±8.6)	294±245 (3.3±2.8)	-1 vs -71

Notes: ^aThis is an open-label extension (OLE) study in patients from CS6, CS16, or newly included patients. Data at 6 months. ^bIncluded patients with FCS. ^cFor CS16, the protocol was amended so that patients that had not already completed ≥5 months of dosing as of 27 May 2016 had dose frequency reduced to 300 mg every 2 weeks or dose reduced to 150 mg per week after 13 weeks of treatment. A total of 39 patients had their dose or frequency of dosing changed as a consequence of this amendment.

heterozygous for *LPL* and *APOA5* or *LMFI* mutations while 14 patients did not have identifiable mutations. They were randomized 1:1 to 52 weeks of weekly subcutaneous volanesorsen (285mg) or placebo.^{71,72} Patients underwent a diet stabilization run-in period comprising <20g fat per day and mandatory alcohol restrictions before randomisation.

The final endpoint was met with a 94% reduction (1804mg/dl: 20.4mmol/L) in TG at 3 months. In the volanesorsen group, TG levels were reduced by 53% at 6 months and 40% at 12 months. The apparent decrease in efficacy was likely driven by dose adjustments and discontinued patients as continued TG measurements were required by the study protocol. Among patients with baseline TG>750mg/dL (8.48mmol/L), 77% vs 10% of patients were classified as responders by achieving this level on treatment. Over 12 months, this occurred in 60% of patients on weekly dosing and 46% of patients on fortnightly dosing schedules compared to 7% of patients on placebo. Adequate response defined as >40% reduction in TGs (based on the efficacy of fibrates) was achieved by 88 vs 9% patients ($p < 0.0001$). ApoC3 levels were reduced by 84% compared with a 6% increase on placebo at 3 months. In the treated group CM TGs were reduced by 83%, apoB₄₈ by 76%, non-HDL-cholesterol (nHDL-C) by 46%, and very-low-density lipoprotein (VLDL)-cholesterol by 58% while HDL-C increased by 46%, and apoA1 by 14%. LDL-C increased by 136% and apoB by 20% indicating significant increased throughput in the apoB₁₀₀ pathway. The effect of volanesorsen on TGs was independent of the genetic diagnosis as TG levels decreased by 65% in the 17 patients with mutations in *LPL* and 75% in 9 patients with non-*LPL* defects.

A composite endpoint for pancreatitis and pain was used for clinical efficacy. Adjudicated acute pancreatitis and abdominal pain occurred in 12 (36%) patients in the volanesorsen group and 13 (39%) patients on the placebo group comprising 2.73 vs 2.04 events/year ($p=0.62$). Pancreatitis was observed in 4 patients on placebo in the study and none on volanesorsen treatment though 1 patient had an attack 9 days after the last study dose. A *post hoc* analysis was conducted in patients with at least 2 episodes of pancreatitis in the previous 5 years. Prior rates of 24 events in 7 patients (volanesorsen) vs 17 events in 4 patients (placebo) changed to zero events on volanesorsen and 4 events in 3 patients on placebo ($p=0.02$). Self-reported abdominal pain intensity was reduced in the

volanesorsen-treated patients (score -2.3 ($n=7$) vs. -1.3 ($n=10$); $p=0.03$).³⁸

Compass (Cs16)

The COMPASS trial investigated the efficacy and safety of volanesorsen in 113 patients with hypertriglyceridemia defined as fasting TG>500mg/dl (5.65mmol/L).⁷³ Recruitment TG levels were far higher at 1261 ± 955 mg/dl (14.3 ± 10.8 mmol/L). Patients were randomised to volanesorsen: ($n=75$ including 5 FCS) or placebo ($n=38$; 2 FCS). All 114 participants (113 dosed) received volanesorsen 285 mg once per week (or less frequently) depending on safety or tolerability reasons. Preliminary results show that after 3 months of treatment TGs were reduced by $73\pm17\%$ in the volanesorsen group compared with $2\pm53\%$ on placebo corresponding to 1869mg/dL (9.8mmol/L) reduction. The 7 patients with FCS had a baseline TG 2280 ± 973 mg/dL (25.8 ± 11.0 mmol/L) and achieved a similar $74\pm14\%$ TG reduction. Pancreatitis events were reduced with volanesorsen therapy (0 vs 6; $p=0.01$) but 1 patient on volanesorsen had pancreatitis 3 months after the last dose.

Extension Study

An ongoing multi-centre phase 3 open-label extension (OLE) of treated subjects includes patients from the CS6 (APPROACH), CS16 (COMPASS index study) and a group of FCS patients who could have been potentially recruited (CS7) is ongoing.⁶⁷ Combined data from COMPASS and APPROACH studies showed a reduction in pancreatitis events with 1 event on volanesorsen (1 patient) compared with 9 events (6 patients) on placebo ($p=0.02$).⁷⁴ TG levels in the APPROACH and COMPASS were reduced by 49% and 65% at 3 months, 55% and 43% at 6 months, and 35% to 40% at 12 months of the OLE study compared to baseline values in the original studies. Reductions in TG (38% and 39%) were maintained up to 18 months. Patients not previously treated with volanesorsen achieved similar reductions in TG levels ranging from 60% to 32% from months 3 to 12.

A global retrospective study of a subset of patients from the APPROACH-OLE extension phase (ReFOCUS study; $n=22$) reported improvements in disease burden after volanesorsen therapy (median 222 days).⁷⁵ More patients reported effective management of FCS symptoms after 3 months of treatment compared to before (19 vs 40%). Almost all reported that their symptoms were controlled with diet (90 vs 55%) after treatment. The number of FCS symptoms was reduced after 3 months of treatment

with volanesorsen (median 6.5 vs 3.5; $p < 0.05$). Reductions were seen in physical (47%, $p = 0.009$), emotional (47%; $p = 0.007$) and cognitive manifestations (46%; $p = 0.03$) but not in pancreatitis admissions. Patients also reported improvements in their personal, social and professional lives with more patients reporting “no interference” (5% to 23%) and fewer patients reporting high levels of interference (59% to 37%).⁷⁵ Overall this suggests an improvement in quality of life with treatment.

Safety and Tolerability

As is typical in phase 3 studies, many patients treated with volanesorsen experienced an adverse event (AE) across the programme.⁶⁷ The most common were events related to local tolerability and decreases in platelet counts.⁷⁶ In the APPROACH (CS6) study an injection site reaction (ISR) was reported by 61% of patients (12% of total drug injections) with volanesorsen compared with none on placebo. One patient withdrew due to an ISR.

The most common reason for discontinuation of volanesorsen treatment in APPROACH (CS6) was due to adverse events (9 patients, 27%) with 5 patients stopping due to platelet reductions and 4 for other reasons. Confirmed low platelet counts ($< 140 \times 10^9/L$) were observed in 25 patients (76%) with volanesorsen and in 8 patients (24%) on placebo while levels $< 100 \times 10^9/L$ were found in 16 patients (48%) on volanesorsen and none in patients who received placebo. Two patients developed severe thrombocytopenia ($< 25 \times 10^9/L$) and discontinued treatment in mid-study. Neither had any bleeding. Platelet levels recovered after 23–33 days following steroid/immunoglobulin therapy. Investigators withdrew 3 other patients from the study for less severe thrombocytopenia.

In the original CS6 protocol, treatment interruption followed by restarting at the original dose of study drug (300 mg/week) was the only permitted option for managing a platelet decline, other than discontinuing treatment. Patients withdrew from the study if they had a second decline in platelets. The platelet monitoring regime and dose adjustment were changed in mid-study. The rate of treatment discontinuations due to platelet reductions, and discontinuations for any reason, were higher before the change in the platelet monitoring and dose adjustment algorithm. No platelet counts $< 50 \times 10^9/L$ were observed in CS6 after the protocol change. In the volanesorsen group, 30% of patients reduced their dosing to fortnightly (weeks 26 and 46) and 33% had dose interruptions because of adverse events or laboratory values mostly

due to platelet reductions. Apart from ISRs and low platelets in CS6, the frequencies of nausea, weakness, myalgia or arthralgia, diarrhea, nose bleeds (epistaxis) and hyperglycaemia (diabetes) were higher in the volanesorsen-treated group.

Aggregated Safety Results

Across the studies, 75% of the AEs were mild in severity, with abdominal pain, nasopharyngitis, fatigue and headache being the most common (> 15). Most volanesorsen-treated patients (82%) in the APPROACH and its OLE experienced ISRs persisting longer than 2 days with at least one symptom of pain, erythema, pruritus or local swelling. These typically occurred early in treatment with a median time to a diagnosed ISR of 4.3 weeks.⁷⁶ In the COMPASS (CS16) study an ISR occurred with 24% of volanesorsen injections. No serious platelet reduction events were seen in the study though one potential SAE of serum sickness occurred 2 weeks after the last study dose.

Across all studies in FCS, in-study discontinuations were recorded by 10 patients receiving volanesorsen across the studies based on multiple AEs at the injection sites; discomfort, pruritus, rash, warmth (1 patient each), discolouration, oedema, (2 patients each), swelling (3 patients), erythema and pain (7 patients each).⁷⁷

Serious Adverse Events in the Aggregated Studies

Serious adverse events (SAEs) were reported in 13% patients with volanesorsen treatment. Three SAEs in 3 (3%) patients were considered treatment-related and included 2 reports of thrombocytopenia ($< 25 \times 10^9/L$) (APPROACH) and a report of serum sickness (COMPASS). Several moderate severity SAEs were reported in APPROACH including abdominal pain (adjudicated as pancreatitis), cholangitis, drug-induced liver injury (following diclofenac), ankle fracture and dehydration. These were seen in one patient (3%) each. In the ongoing APPROACH-OLE, 13 patients (19%) (10 treatment naïve, and 3 previously treated) reported a serious adverse event (SAE).⁷⁷ During these studies, 4 cases of pancreatitis and 1 case of proteinuria were observed. Events of juvenile idiopathic arthritis, reduced platelet count or severe thrombocytopenia and proteinuria were considered related to study drug.⁷⁶ Treatment was discontinued due to severe thrombocytopenia in 4 patients.

Anti-drug antibodies were reported positive in 16% and 30% of volanesorsen-treated patients in the APPROACH and COMPASS studies, respectively, but were not associated with safety concerns or reduced drug efficacy based on the limited data available.⁷⁶

Familial Partial Lipodystrophy (BROADEN)

A study of the efficacy of volanesorsen was conducted in 15 patients with FPLD with moderate glycaemic control ($HbA_{1c} >7.5\%$ (58mmol/mol)) and hypertriglyceridaemia (200–500mg/dl; 2.26–5.65mmol/L).⁷⁸ Patients were randomized (2:1) to weekly subcutaneous treatment with 300 mg of volanesorsen or placebo for 13 weeks in a phase 2 study. Volanesorsen treatment decreased apoC3 by 88% and TG levels by 69% with an increase HDL-C of 42%. Insulin sensitivity improved by 50% and HbA_{1c} decreased by 3.4 mmol/mol (0.44%) paralleling changes in fructosamine and glycated albumin. Changes in insulin resistance correlated with reductions in apoC3 ($r = -0.61$, $p=0.03$) and TGs ($r = -0.68$, $p=0.01$). The majority of adverse events reported were mild and no discontinuations occurred.

Discussion

Volanesorsen

The observational relationship between severe hypertriglyceridemia, particularly chylomicronaemia, and acute pancreatitis is well established. Patients with FCS have many documented complications from sustained chylomicronaemia, including commonly acute pancreatitis.^{4,20,28,39} This condition is an orphan disorder with a poor response to many current treatments. The clinical studies with volanesorsen have demonstrate a profound impact on the chosen surrogate outcomes of reductions in apoC3 and triglyceride levels (30–70%) which are maintained up to 18 months.⁷² These were accompanied by improvements in patient well-being⁷⁵ and a reduction in the rate of pancreatitis events though none of the studies were powered for this endpoint and all comparisons made either involved short-term trial data or were with retrospective patient-matched case records.⁷⁴

The volanesorsen studies have also shown a high rate of discontinuation (up to 30%), problems with injection site reactions. Platelet levels have also been a problem in these studies. In the CS6 APPROACH study, a number of patients had initially low platelet levels but this was not seen in the other volanesorsen trials. Furthermore, volanesorsen treatment was associated with an unpredictable poorly

understood side-effect of thrombocytopenia that has required dose interruption, change of administration schedules or drug discontinuation. The time course of thrombocytopenia seemed to indicate a chronic effect possibly correlated with drug accumulation as it responded in many cases to dose interruption. Whether this is a compound or target (apoC3) specific effect is unclear. Cases of thrombocytopenia and bleeding have also been recorded with niacin which also reduces triglyceride and apoC3 levels^{79,80} but also with other ASOs with similar structural characteristics to volanesorsen such as inotersen (an ASO to transerythrin used to treat amyloidosis).⁸¹ The effect may be related to an underlying immune dysfunction.⁸¹

Protocols for volanesorsen administration have been modified after the initial phase 3 studies to include a reduction in dosing to fortnightly after an initial weekly administration loading phase and an additional mandatory requirement for long-term platelet monitoring. The recommended starting dosage is 285 mg once weekly for 3 months, followed by down-titration to a maintenance dosing schedule of once every 2 weeks. If a 25% reduction in TG levels is not achieved, or if TG remain >2000 mg/dl (22.6 mmol/L) at 3 months, treatment should be stopped.

Regulatory authorities have taken differing views of the data available on 312 patients of whom 248 were treated with volanesorsen. This includes 86 patients with FCS. The US Food and Drug Administration (FDA) refused to approve volanesorsen for the treatment of patients with FCS based on safety issues of thrombocytopenia and risks of bleeding (8/2018).⁸² In contrast, the European Medicines Agency (EMA) (02/2019) gave conditional marketing authorization of the drug for patients with confirmed FCS who are at high risk of pancreatitis in whom there is inadequate response to TG reduction therapy and diet provided that extra data were gathered in a registry study.⁷⁶ All these bodies noted differences in the dose requested for approval compared to that used in the phase 3 studies and that randomised controlled trial data on the efficacy and safety data for the new lower proposed dose were lacking. Thus, they requested additional registry data on safety and efficacy is gathered on patients continuing on volanesorsen.

Among payer organisations, the National Institute for Health and Care Excellence (NICE) in the UK (1/2020) performed a systematic review of the evidence base for FCS, its consequences and the cost-effectiveness of volanesorsen.⁸³ NICE noted that uncertainty existed about the relationship of the rate of recurrent acute pancreatitis in FCS with TG levels as some patients with FCS experience pancreatitis events at

lower TG levels than those seen in patients with raised TGs from other causes. Hospital admissions data in FCS are also not completely reliable as many patients self-manage to avoid admission by fasting when they recognise symptoms of pancreatitis so admission events likely only represent the most serious events. The composite endpoint of pancreatitis admissions and abdominal pain attempted to compensate for this but adds a substantial subjective component- the use of days fasting (or nil by mouth on admission) might have been better. The design of the pivotal efficacy trial (APPROACH) allowed entry of patients who had previously received alipogene tiparvovec over 2 years before⁷¹ and 11% of patients recruited had previously received this gene therapy. Steroid, niacin or anti-psychotic therapy were contra-indications to recruitment. The inclusion of alipogene-tiparvovec-treated patients may have reduced the rate of pancreatitis seen in the CS6 study thus understating its true effects.⁸⁴

The long-term effectiveness of volanesorsen was also unclear as a diminution of response seen in APPROACH-OLE compared to the APPROACH study. This was further complicated by its design as a self-selected admixed sub-study compromised by high rates of drug discontinuation in the original study. The draft guidance from the highly specialised therapies (orphan diseases) did not recommend volanesorsen for use in the National Health Service in England for treating FCS at its suggested marketed price as its cost-effectiveness exceeded the £100,000/year quality-adjusted life year (QALY) threshold used by this committee. Further negotiations are underway about patient access schemes. Patients are already receiving volanesorsen in some countries based on compassionate use (USA) or early access to medicines schemes (UK).

The current programme for volanesorsen may be superseded by new developments. Tolerability has been noted to be a problem with ASOs and a new liver-targeted technology based on high first-pass liver extraction (through the asialoglycoprotein receptor) of modified small interfering RNA molecules may allow doses of active agents to be reduced while preserving efficacy and reducing adverse events.⁸⁵ AKCEA-APO-CIII-L_{Rx} is a third-generation ligand-conjugated antisense (LICA) drug comprising an ASO to apoC3 with a N-acetylgalactosamine-containing adduct (GalNac) to increase first-pass hepatic clearance. The LICA technology may lower the risk of thrombocytopenia given its higher tissue selectivity and more flexible dosing possibilities including lower dose options due to its longer half-life.⁸⁶ A dose-ranging study of 10, 30, 60, 90, or 120 mg of AKCEA-APOCIII-LRx in healthy volunteers showed reductions of 0,

42%, 73%, 81%, and 92% in apoC3, and 12%, 7%, 42%, 73%, and 77% in TGs after 14 days. In a multiple-dose study, patients received 15mg and 30mg weekly or 60mg every 4 weeks. Reductions of 66%, 84%, and 89% in apoC3, and 59%, 73%, and 66% in TGs were observed 1 week after the last dose had been administered. A placebo-controlled trial of IONIS-APO-CIII-L_{Rx} (ISIS 678354) for reduction of TGs in patients with hypertriglyceridaemia is underway. This modification may provide a solution to safety concerns about volanesorsen.

Therapeutic Competitors

A number of other therapeutic approaches have been taken to treat patients with FCS.

Gene therapy using an adeno-associated virus (AAV) vector and intra-muscular injection allied with short-term immunosuppressive therapy has been tried. Alipogene Tiparvovec (Glybera) had to dose at its maximum available dose and reduce total triglycerides transiently but had greater effects on new CM production. It showed up to a 50% reduction in pancreatitis events after 2 years.^{84,87} Its effectiveness was restricted to patients with LPL mutations and administration involved multi-point intra-muscular injections under general anaesthetic allied with temporary immunosuppressant therapy. It had a high front-end costs of 1,000,000 Euro per patient with a planned 5-year payment model.^{88,89} After 1 patient had been treated in Europe, this therapy was discontinued on commercial grounds.

As upregulation of apoC2 seems to inhibit the action of apoC3, a novel apolipoprotein-derived peptide therapeutic has been devised as an apoC2 mimetic (D6PV).⁹⁰ This peptide reduced TG by 80% in both apoC2-deficient mice and human apoC3-transgenic mice. In hApoC3-Tg mice, D6PV reduced apoC3 by 80% and apoB by 65%. Whether this mimetic peptide is capable of use in man remains to be determined.

Previous studies have investigated therapies that interfere with cholesterol and triglyceride loading of CM and VLDL precursors. Lomitapide, a microsomal triglyceride transfer protein (MTP) inhibitor, is licensed for treatment of homozygous familial hypercholesterolaemia (HoFH) but is known to cause hepatic dysfunction.⁹¹ One patient with FCS was treated with lomitapide for 13 years achieving a 75% reduction in TGs, a reduction in pancreatitis admissions but unfortunately developed hepatic fibrosis.⁹² A different approach has been to inhibit intra-cellular triglyceride synthesis from diglyceride precursors which is a feature of CM and VLDL production. Pradigastat (LCQ908) is a diacyl-glycerol-acyl transferase-1 (DGAT-1) inhibitor. A phase 2 study of 6 patients with FCS using 10–40mg pradigastat showed that the 20mg and 40mg

doses reduced TGs by 33% and 54%.⁹³ This effect was driven by reductions in post-prandial TGs, CM production and apoB₄₈ levels. No significant excess adverse events were seen over the 3-week study but this drug does not seem to have progressed in development.

Alternative drug targets in FCS include ANGPTL3 and ANGPTL4. ANGPTLs regulate triglyceride metabolism⁶³ and loss of function variants and patients homozygous for ANGPTL3 deficiency are associated with lower TG levels and reduced rates of cardiovascular disease.^{94,95} Both ASO (AKCEA-ANGPTL3-L_{Rx}) and antibody interventions (evinacumab) have been developed with ASOs showing reductions of 33–60% in dose-ranging studies.⁹⁶ Evinacumab, an anti-ANGPTL3 antibody, has been shown to reduce cholesterol in HoFH⁹⁷ and is now in trial in patients with FCS as it reduced triglycerides by up to 76% in initial studies.⁹⁴ In a dose-ranging study in patients with hypertriglyceridaemia evinacumab reduced TGs by 77% at 10mg/kg and 83% at 20mg/kg. Further studies are now underway with evinacumab. Other approaches to targeting ANGPTL include Clustered Regularly Interspaced Short Palindromic Repeats; CRISPR-associated protein-9 (CRISPR/Cas9) gene inactivation.⁹⁸

In FPLD alternatives to volanesorsen treatment also exist. Some patients respond to new higher dose insulin formulations^{4,49} while specific adipocyte hormone therapies such as metreleptin which directly target the dysfunctional adipocytes may have a role.⁹⁹

Conclusion

Familial chylomicronaemia syndrome is an orphan disorder where current treatment is inadequate and health burdens caused by pancreatitis are high. Inhibition of apoC3 using the ASO reduces triglyceride levels by up to 77% and rates of pancreatitis while improving well-being. Its adverse effect profile including a high rate of injection site reactions and especially its unpredictable adverse effect of causing thrombocytopenia has led to modifications in its approved dosing schedule that have so far limited its approval outside of compassionate use. Further developments in ApoC3 inhibition may result in improved safety-efficacy profiles and other approaches to FCS are also in early trials. It is likely that FCS will become a treatable disorder in the near future.

Disclosure

Professor Wierzbicki has chaired lipid and other guideline groups at the National Institute for Health and Clinical Excellence (NICE) and was an external specialist adviser for the review of volanesorsen (ID1326). He was also an external

specialist assessor of volanesorsen for the European Medicines Agency (EMA). The views expressed in this article are his own and do not represent those of NICE or the EMA. He is a site investigator for studies of volanesorsen and evinacumab in FCS. The authors report no other conflicts of interest in this work.

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