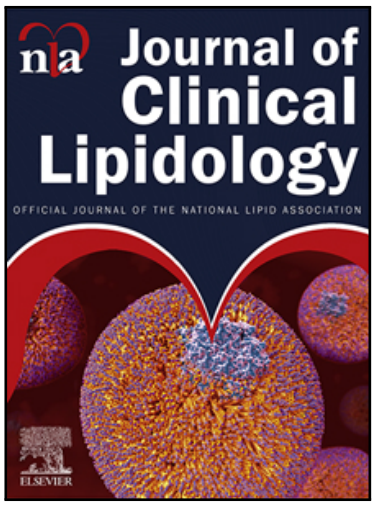

Real life evidence of volanesorsen for Familial Chylomicronemia Syndrome in Colombia.

Alejandro Román-González M.D. , Alejandro Castellanos M.D. , Diego Perdomo , Christian Colón , Juan Jose Vargas , Carlos O. Mendivil M.D. , Johnayro Gutierrez

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Highlights

- FCS is a rare condition associated with severe hypertriglyceridemia, abdominal pain and recurrent pancreatitis episodes
- There is limited real-life evidence of volanesorsen for the treatment of FCS. This study presents evidence from a middle-income country regarding efficacy and safety of volanesorsen for FCS
- Long-term follow-up studies are needed to define the impact of volanesorsen for FCS: Additionally, new therapies in development will improve the safety of this type of treatments

Real life evidence of volanesorsen for Familial Chylomicronemia Syndrome in Colombia.

Alejandro Román-González, M.D.[1,2], Alejandro Castellanos. M.D.[3], Diego Perdomo[4], Christian Colón[5,7], Juan Jose Vargas[6], Carlos O. Mendivil, M.D., [7], Johnayro Gutierrez[1,8]

1. Endocrinology and Diabetes Section, Internal Medicine Department, Faculty of Medicine, Universidad de Antioquia
2. Hospital San Juan de Dios, Rionegro, Antioquia
3. Medicina Interna, Hospital San Jerónimo de Montería, Universidad del Sinú Elias Bechara Zainum, Montería, Colombia
4. Centros Médicos Colsanitas, Bogotá, Colombia
5. Hospital Universitario Fundación Santa Fe de Bogotá, Bogotá, Colombia
6. Clínica Especializada La Concepción, Sincelejo, Colombia
7. School of Medicine, Universidad de los Andes, Colombia. Section of Endocrinology, Fundación Santa Fe de Bogotá, Colombia
8. Clínica Somer, Rionegro, Antioquia.

Correspondence

Alejandro Román-González, M.D

Universidad de Antioquia-Hospital San Vicente Fundación

Medellín, Colombia

Abstract

Background: Familial Chylomicronemia syndrome (FCS) is an ultrarare disorder associated with pathogenic variants in genes implicated in chylomicron metabolism such as *LPL*, *APOA5*, *APOC2*, *GPIHBP1* and *LMF1*. Patients with FCS have severe hypertriglyceridemia complicated with recurrent episodes of pancreatitis. Volanesorsen is a treatment option for such patients. However, this treatment is not approved or available in all countries.

Objective: To present the real-life evidence of clinical response to volanesorsen in patients with FCS in Colombia.

Methods: All patients treated with volanesorsen in Colombia as of June 25, 2024, were included. After informed consent, relevant clinical and laboratory data were obtained through review of clinical charts and records from the volanesorsen patient support program.

Results:

Ten patients with FCS and treated with volanesorsen were included. Most cases were caused by variants in *LPL*. 90% of cases had at least one episode of pancreatis, the mean number of pancreatitis was five. Median follow-up was 56.5 weeks (IQR 38.3-82.3). The median highest plasma triglyceride (TG) before treatment was 3111 mg/dL (IQR 1738-3810), while median lowest TG levels after treatment were 493 mg/dl (IQR 147-812). The mean percent decreases in plasma TG at months 1, 3, 6 and 12 were respectively 53.6%, 59.7%, 51.5% and 40,5%, respectively. There were no new pancreatitis episodes after

initiation of volanesorsen treatment. Side effects were consistent with those reported in clinical trials.

Conclusion

Real-life data of volanesorsen treatment for FCS in Colombia demonstrate efficacy and safety similar to pivotal clinical trials.

Introduction

Familial Chylomicronemia Syndrome (FCS) is an extremely rare genetic disorder caused by variants in lipoprotein lipase (*LPL*) and associated genes (*LMF1, APOA5, APOC2, GPIHBP1*)(1-4). The majority of cases are due to pathogenic variants in *LPL*, with less frequent occurrences in the other genes (5, 6). This disease is characterized by severe hypertriglyceridemia, which leads to recurrent episodes of pancreatitis (7-9). In addition to these physical complications, patients with FCS experience multiple emotional and cognitive symptoms, with abdominal pain being one of the most prominent and distressing features (10). Consequently, FCS patients face declining mental well-being, strained social relationships, limitations in employment opportunities, and difficulties adhering to a strict, low-fat diet (8-10).

The treatment of FCS is challenging due to the limited efficacy of currently available pharmaceutical options (3, 11). Patients respond insufficiently or not at all to treatment with fibrates or omega-3 fatty acids, and adherence to the required low-fat diet is hindered by its poor palatability and tolerance. As a result, there was a need for new therapeutic approaches, and volanesorsen emerged as a treatment option for FCS (12-15).

Volanesorsen is an antisense oligonucleotide that targets the mRNA of apolipoprotein C-III (apoC-III) and has been approved in certain regions for the treatment of FCS (16). This drug reduces plasma levels of apoC-III, TG, and chylomicrons, and its use has been associated with a reduction in pancreatitis episodes (17). A recent meta-analysis of three randomized, controlled trials of volanesorsen demonstrated fewer pancreatitis episodes in patients treated with volanesorsen compared to placebo (OR, 0.18; 95% CI, 0.04 to 0.82) (17). Additionally, volanesorsen has been shown to reduce the overall burden of FCS (18).

An analysis of the ReFOCUS study indicated improvements in physical, emotional, and cognitive domains in patients receiving volanesorsen treatment (18).

However, there is limited real-world data on the long-term use of volanesorsen. Some studies, including extensions of the phase 3 APPROACH and COMPASS trials, have shown that volanesorsen is effective in decreasing TG levels by approximately 50% after one year of treatment (19). The most common side effects reported include injection site reactions and a decrease in platelet count (19). Recent data from the UK Early Access to Medicine Scheme also indicated an approximately 50% decrease in TG levels in 22 patients with FCS over 6 to 51 months, along with a reduction in pancreatitis event rates and a decrease in platelet count, though no cases of severe thrombocytopenia were observed (20).

In this study, we present real-world data on the use of volanesorsen in patients with genetically confirmed FCS in Colombia. This study provides a unique opportunity to assess the impact of volanesorsen in a middle-income country like Colombia, which has nearly universal healthcare access but limited access to volanesorsen, with approvals granted on a case-by-case basis.

Materials and methods

All adult patients treated with volanesorsen in Colombia were included. Relevant demographic, clinical and laboratory information was extracted through review of clinical charts and records from the volanesorsen patient support program. The study was approved by the Ethics Committee of Hospital Universitario San Vicente Fundación, Medellín, Colombia. Patients included in the study were followed up to June 25, 2024.

Biochemical analysis, safety monitoring and patient follow-up.

Measurements of TG and platelet counts were performed by standard methods before treatment, weekly for the initial three months of treatment and monthly thereafter. The volanesorsen patient support program staff monitored all laboratory values and communicated with treating physicians in case of adverse events or low platelet counts.

Statistical analyses

Statistical analyses were carried out in SPSS Statistics 25.0 (Armonk, New York, IBM Corp). Data are presented as medians and interquartile ranges (IQR, p25-p75). The primary outcome was the changes in the plasma TG values from baseline to month 1, month 3, month 6 and month 12 after volanesorsen initiation. Secondary outcomes included the absolute change from highest to the lowest TG values and changes in platelet counts. Treatment effects were analyzed using paired t-test or Wilcoxon signed rank test where applicable. Statistical significance was defined at the 5% level.

Industry Support and Access to Volanesorsen:

The Colombian healthcare system provided coverage for volanesorsen through a special access program for patients with orphan diseases. This program requires genetic

confirmation of the orphan disease and regulatory approval of the treatment on a case-by-case basis. As part of this process, the Colombian healthcare system classified volanesorsen as a "vital drug not available" and covered its treatment costs for the patients included in this study.

PTC Therapeutics did not fund this study, which was independently designed and conducted by the researchers. However, all authors involved in this manuscript have professional ties to PTC Therapeutics, including speaker fees, participation in symposia, travel expenses for medical conferences, and the organization of medical education meetings in Colombia. These meetings provided opportunities for the investigators to discuss various research programs related to familial chylomicronemia syndrome (FCS) in the country.

Additionally, the patient support program is managed by an independent company contracted by PTC Therapeutics, as required by the Colombian government. This ensures the safety and monitoring of drugs that are not widely available for treating orphan diseases.

Results

Ten patients were included, six females and four males. The median age at the start of volanesorsen treatment was 42.5 years (IQR 25.7-56.2). The gene most frequently affected was *LPL* (70%), two cases had variants in *APOA5* (20%), one of them was a double heterozygous for variants in *APOA5* and *GCKR*, and one case had a variant in *GPIHBP1* (10%). 90% of cases had at least 1 episode of pancreatis, with a mean number of pancreatitis of 4.9 (range 0-16). (Table 1). All patients were treated before volanesorsen treatment with other pharmacology options such as fibrates and/or omega 3 fatty acids. Among the 10 cases included in this study, two pairs of patients were siblings. Case 9 (female) and Case 10 (male) are siblings, as are Case 7 and Case 8 (both male). Case 5 is unrelated to any other cases but originates from the same geographic region in Colombia. The remaining cases are not related to one another.

Follow up

Median follow-up was 56.5 weeks (IQR 38.3-82.3) and was continued until June 25, 2024, when the database was closed. The median number of volanesorsen doses was 22 (IQR 18-30). The median number of missed doses due to local authorization and administrative issues during the treatment period was 4 (IQR 7-19).

Effectiveness of treatment

Median highest TG values before treatment were 3111 mg/dL (IQR 1738-3810), while median lowest triglycerides levels after treatment were 493 mg/dL (IQR 147-812) ($p<0.005$). Baseline median pretreatment triglyceride levels were 1663 (IQR 571-1294), 771 at month 1 (n=10) (IQR 571-1294), 670 (IQR 542-1101) at month 3 (n=8), 806 (IQR

490-1045) at month 6 (n=9), and 990 (IQR 764-1308) at month 12 (n=6). All decreases in TG levels were statistically significant (p=0,021). The mean percent decreases at months 1, 3, 6 and 12 were respectively 53.6%, 59.7%, 51.5% and 40.5%. Similarly, the mean absolute changes at months 1, 3, 6 and 12 were respectively 892 mg/dL, 993 mg/dL, 857 mg/dL and 673 mg/dL (Figure 1A and 1B). The percentage of patients achieving triglyceride levels below 750 mg/dL at each time point were as follows: Month 1, 50% (n=10); Month 3, 62.5% (n=8); Month 6, 33.3% (n=9); and Month 12, 16.6% (n=6). There were no pancreatitis episodes after the initiation of volanesorsen treatment. (p<0.007)

Safety

The median initial platelet count was 215000/mm3 (IQR 148000-369000), and the median last platelet count was 168000 (IQR 122000-225500). The median lowest platelet count was 110000 (IQR 86500-145000), a non-statistically significant decrease (p=0.051). One patient had an initial platelet count below 140000. The percentage of patients reaching a platelet count below 140000/mm3 during treatment was 60%. The proportion of patients reaching platelet counts between 75000 and 100000 was 20%. According to Common Terminology Criteria for Adverse Events 5.0, there was no grade 2-5 platelet count decrease. No patient required dose modification due to platelet count changes. Other side effects were present in 80% of cases, the most common being local site reactions in (40%), followed by cough (30%), abdominal complaints (20%), fever (20%), facial edema (10%) and headache (10%). One patient from withdrew treatment due to a personal decision. This patient presented a clinical picture characterized by lower limb edema, myalgia, muscle weakness, arthralgia, fatigue, and walking limitation. The medication was temporarily withdrawn and the patient was hospitalized and a diagnosis of systemic lupus

erythematosus (SLE) was made. She received glucocorticoids with resolution of the condition. Three months later she restarted the volanesorsen but stopped it 2 months later by her own decision.

Discussion

This study evaluated real-life data of volanesorsen for the treatment of FCS in a Colombia, a medium income country. To our knowledge, few studies have evaluated real-life data in this setting (20). We found that volanesorsen treatment reduced TG levels to a similar extent compared to pivotal clinical trials(14, 15, 21, 22). The mean percentage decrease change in TG was around 50% during most of the follow-up. We observed a slight increase in TG at month 12, which may be explained by losses to follow-up in four patients, and also to missed doses. This last situation may be explained by limitations in authorization of volanesorsen due to administrative issues. In Colombia, volanesorsen is still not approved for commercialization by regulatory agencies. Therefore, its use must be authorized on a case-by-case basis based on lack of response to other medical treatments, and of a genetic evaluation for FCS. Each case must be presented to the Colombian regulatory agency, INVIMA, and if approved, the medication is imported for each individual case. This process is quite slow and complicated, limiting patient access to a potential life-saving treatment.

We also observed not only improvement in TG but also in the number of pancreatitis episodes. After volanesorsen treatment, no patient presented a new pancreatitis event, similar to what was observed in a recent meta-analysis (17). The decrease in pancreatitis episodes may be related to decrease in ApoCIII levels (23). However, the sample size of this study is small. While the absence of new pancreatitis episodes is encouraging, longer follow-up and specifically designed trials are necessary to robustly assess this clinical outcome.

Volanesorsen treatment was accompanied by a decrease in platelet count, but no patients presented grade 2 or higher thrombocytopenia. Close monitoring of platelet counts is essential during volanesorsen treatment, and dose adjustments or temporary discontinuation may be required to mitigate the risk of severe thrombocytopenia. The development of new approaches to tissue-specific delivery of antisense oligonucleotides (ASO) may prevent or attenuate this adverse effect. This is the case for olezarsen, a new ASO also directed at the apoC-III mRNA, but conjugated with *N*-acetyl galactosamine, which binds to asialoglycoprotein receptors expressed only in hepatocytes (3, 24, 25). The most common side effect was related to injection site reactions as have been reported (22). In the patient with SLE, we are still waiting for the results of anti-histone antibodies to confirm a drug-induced SLE.

The familial relationships identified in this cohort highlight the genetic basis of the condition under study, as two pairs of siblings were included. These familial cases likely share common genetic mutations, potentially influencing the phenotypic expression and response to treatment. This genetic overlap may have led to similarities in clinical presentations and outcomes within the sibling pairs. In contrast, Case 5, while unrelated to the other cases, hails from the same geographic region as Cases 9 and 10, which might reflect a founder effect in this region. The inclusion of familial cases underscores the importance of considering genetic predispositions when interpreting the data. However, the small number of cases and limited representation of familial relationships prevent broader generalizations. Further studies with larger cohorts are needed to explore the influence of familial clustering on the disease's clinical course and response to therapy.

This study has several limitations. This is a retrospective real-life study with no comparison group, with the well-known caveats of this type of approach. Also, the participation of different centers implies differences in the overall clinical approach to a particular patient with FCS. Nonetheless, the effectiveness of the agent compared to available alternatives is so much greater, that the confounding effect of other concomitant therapies is unlikely to have affected the observed results to a relevant extent. Another important limitation is the small number of patients, albeit for such rare disease, ten genetically confirmed patients may represent a considerable sample.

Conclusions

Real-life data of volanesorsen treatment for FCS in Colombia show similar efficacy and safety compared to pivotal clinical trials.

Funding

This study had no dedicated funding

Use of AI and AI-assisted technologies

The authors declare that no AI-assisted technology was used during the writing process.

Data availability

The data supporting the findings from this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

Alejandro Román-González: Speaker fees from PTC therapeutics, Sanofi, Biotoscana, ACE, Ultragenyx, Roche, Novo Nordisk, International Atherosclerosis Society, Amgen, Chiesi, Recordati, Knight, Boehringer. Research support: Amgen, Sanofi

Alejandro Castellanos: Speaker fees PTC therapeutics

Diego Perdomo: Speaker fees PTC therapeutics, Novo Nordisk, Sanofi, Amgen, Novartis

Christian Colón: Speaker fees PTC therapeutics, Abbott, Amgen, AztraZeneca, Bayer, Boehringer Ingelheim, Medtronic, Merck, Novartis, Novo Nordisk, PTC, Sanofi

Juan Jose Vargas: Speaker fees PTC therapeutics.

Carlos O. Mendivil: Scientific advisor for: Abbott, PTC Therapeutics, Procaps, Mitotherapies, NovoNordisk, Procter & Gamble, Team Foods. Speaker for: Abbott, Amgen, AstraZeneca, Bayer, Beckman Coulter, Boehringer Ingelheim, Colmédica, Jannsen, MSD, Novamed, Pfizer, Procter & Gamble, Sanofi.

Johnayro Gutierrez: Speaker fees PTC therapeutics, Sanofi, Novo Nordisk, Ultragenyx, Amgen, Novartis, Recordati.

Credit authorship contribution statement

Alejandro Román-González: writing, review and editing, investigation, conceptualization, formal analysis.

Alejandro Castellanos: writing, review and editing, conceptualization

Diego Perdomo: writing, review and editing, conceptualization

Christian Colón: writing, review and editing, conceptualization

Juan Jose Vargas: writing, review and editing, conceptualization

Carlos O. Mendivil: writing, review and editing, conceptualization

Johnayro Gutierrez writing, review and editing, conceptualization

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Ethics statement

Our research has adhered to relevant ethical guidelines. All patients in this study signed informed consent to use volanesorsen as this is a requirement from the Colombian Agency for medical treatments INVIMA. The study protocol was approved by the authors institution.

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Figure 1A and Figure 1B legend and tittle

Figure 1A: Title: **Percent change in triglyceride levels from baseline (median 1663 mg/dL).**

Legend All decreases in TG levels were statistically significant (p=0,021).

Figure 1B: Title: **Absolute change in triglyceride levels from baseline (median 1663 mg/dL)**

Figure 1A.

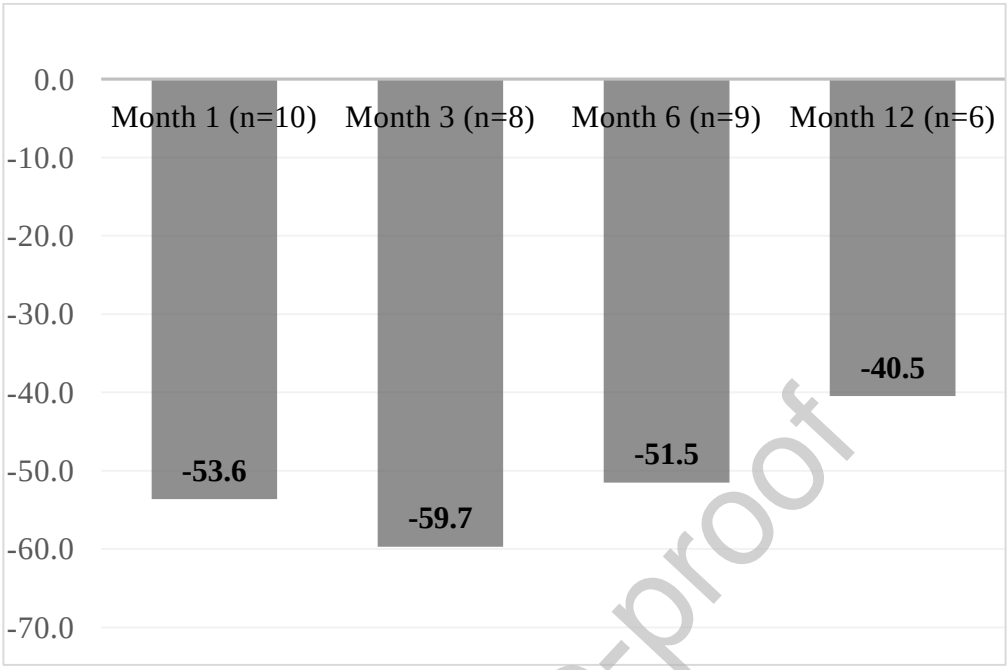

Figure 1B.

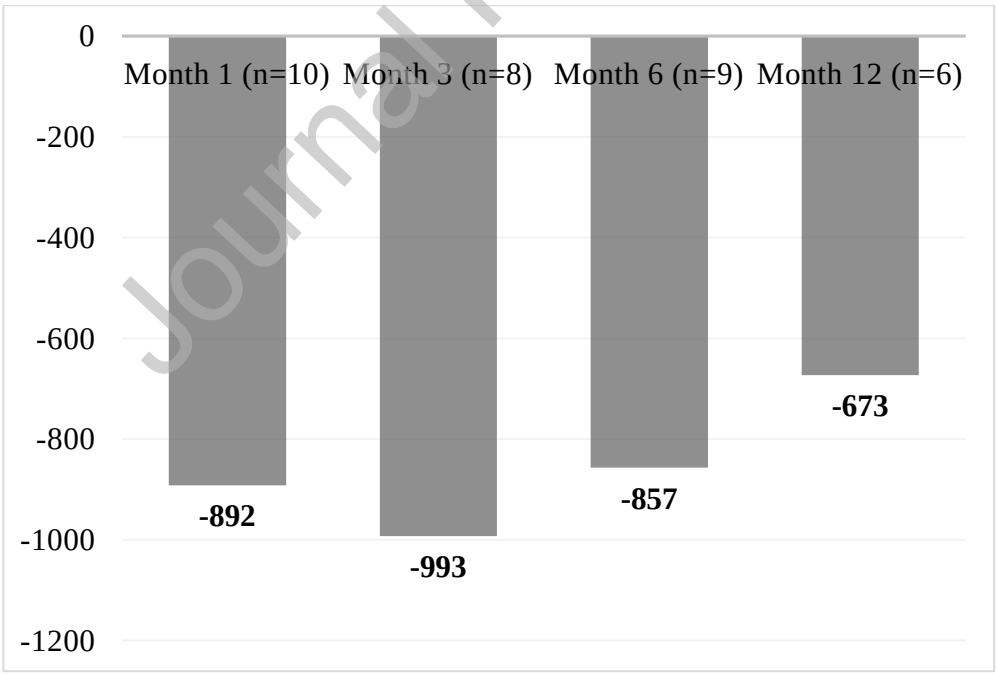

Table 1. Characteristics of the population.

Patient	Age at start of volanesorsen	Sex	Weight (kg)	Height (meters)	BMI	Variant	Pancreatitis episodes before treatment	Age at first pancreatitis episode	LLT before volanesorsen	LLT after volanesorsen	Tg levels before volanesorsen treatment (mg/dL)	Tg one month after treatment	Duration of treatment (weeks)	Basal platelet count
1	54	F	51,7	1,49	23,3	Homozygous *GPIHBP1* c.460_461delGCinsAAA p.Ala154lysfsTer153	16	16	Fenofibric acid/rosuvastatin 135/20 mg OD, ezetimibe 10 mg once daily, Eicosapentaenoic acid 2 gr q12H.	Fenofibric acid/rosuvastatin 135/20 mg OD	3657	636	33	245 000
2	63	M	66	1,72	22,3	Homozygous *LPL* c.88+1G>T	1	30	Gemfibrozil 600 mg Q12H 1200 mg día, Eicosapentaenoic acid 2 gr q12H	Eicosapentaenoic acid 2 gr Q12H Ciprofibrate 100 mg QD	1589	1294	53	314 000
3	51	F	60,2	1,58	24,1	Homozygous *APOA5* c.94T>C, p.Ser232Pro	1	48	Fenofibric acid/rosuvastatin 135/20 mg OD, ezetimibe 10 mg once daily, Eicosapentaenoic acid 2 gr q12H.	None	529	136	60	Data not available
4	27	F	59	1,58	23,6	Homozygous *LPL* c.664G>A p.Gly215Glu	2	27	Plasmapheresis (pregnant patient), then fenofibrate 200 mg QD	None	2094	1365	82	184 000
5	30	F	47	1,45	22,4	Homozygous *LPL* c.664G>A p.Gly215Glu	10	21	Eicosapentaenoic acid 2 gr Q12H, gemfibrozil 600 mg Q12H.	Eicosapentaenoic acid 2 gr Q12H, gemfibrozil 600 mg Q12H.	2648	1074	80	404 000
6	22	F	52,8	1,65	19,5	Double heterozygou	2	21	Rosuvastatin -	Gemfibrozil	1408	151	190	334 000

						s *APOA5* c.(50-1)(161+1_162-1)del *GCKR* c.307G>A; p.Val103Met			20 mg QD, Omega-3 FA (EPA+DHA) - 5,280 mg/d, Gemfibrozil 1800 mg QD	1200 mg QD				
7	21	M	62	1,62	23,6	Compound heterozygous *LPL* c.664G>A, p.Gly215Glu *LPL* c.268_269del, p.Ser90LeufsTer57	0	NA	Gemfibrozil 600 mg Q12H	Gemfibrozil 600 mg Q12H	1225	615	83	148 000
8	41	M	67	1,7	23,2	Compound heterozygous *LPL* c.664G>A p.Gly215Glu *LPL* c.268_269del; p.Ser90LeufsTer57	15	20	Fenofibrate 100 mg QD, Atorvastatin 80 mg QD	Fenofibrate 100 mg QD	4644	3222	40	980 00
9	44	F	49	1,5	21,8	Homozygous *LPL* c.664G>A, p.Gly215Glu	1	30	Gemfibrozil 600 mg Q12H	Gemfibrozil 600 mg Q12H	1738	571	40	148 000
10	64	M	80	1,77	25,5	Homozygous *LPL* c.664G>A, p.Gly215Glu	1	29	Fenofibric acid QD	Gemfibrozil 600 mg Q12H	733	906	11	215 000

BMI: Body mass index. LLT: lipid lowering therapies. Tg: triglycerides, OD: Once daily, Q12H: every 12 hours