A Phase 2 Trial of the Efficacy and Safety of Evinacumab in Patients with Severe Hypertriglyceridemia

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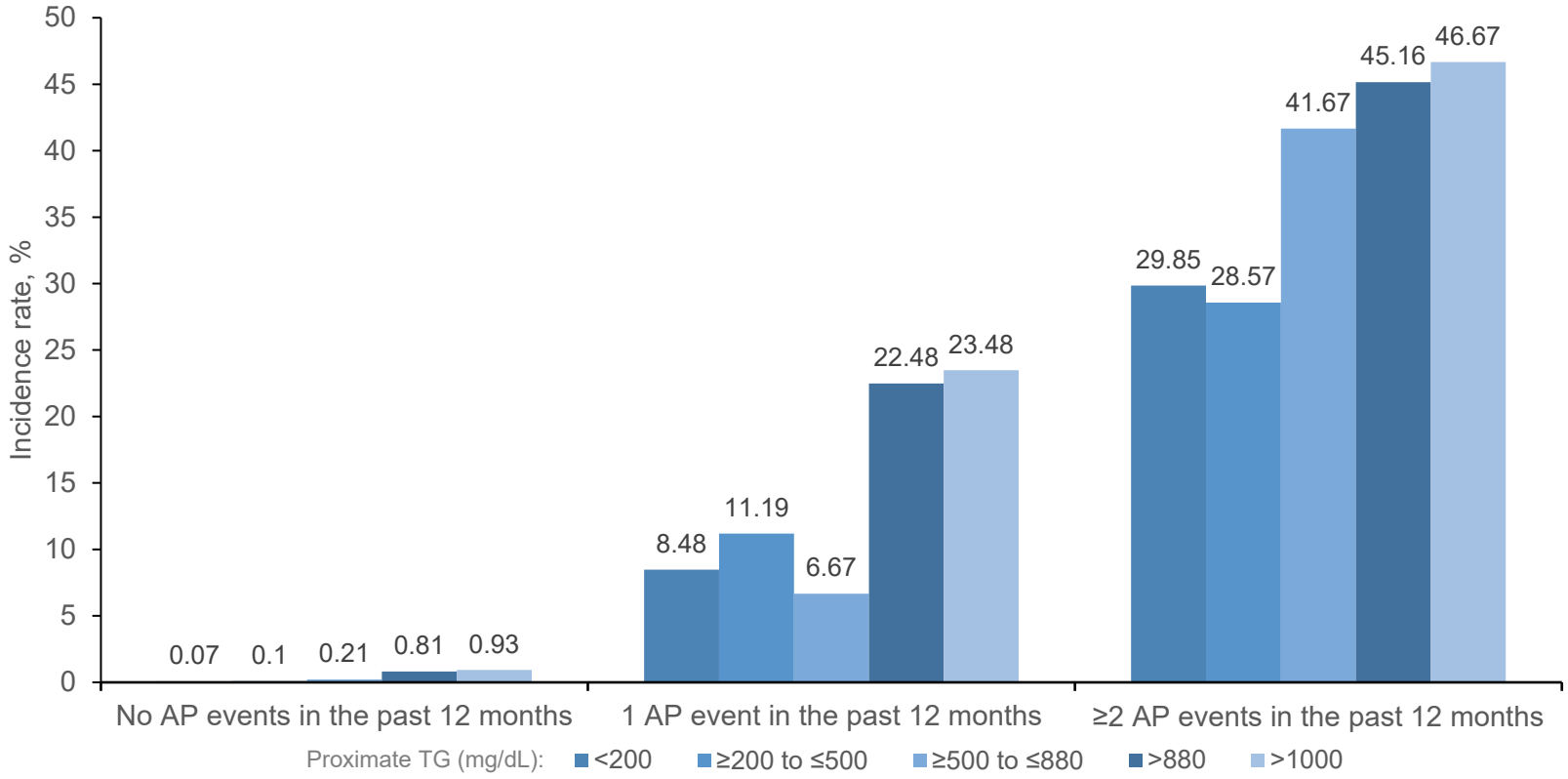
Background

- sHTG, defined as fasting TGs ≥500 mg/dL, is a causal risk factor for AP[1]
- Patients with sHTG-related AP often have recurrent attacks requiring repeat hospital admissions, with worse outcomes than those with non-hypertriglyceridemia-related AP



AP, acute pancreatitis; sHTG, severe hypertriglyceridemia; TG, triglyceride.

Background

- ANGPTL3, an important regulator of lipid metabolism, acts by inhibiting lipoprotein lipase and endothelial lipase[3-5]
- Individuals with LOF variants in ANGPTL3 have demonstrated significantly reduced TGs and other atherogenic lipoproteins[6,7]
- Evinacumab, a fully human monoclonal antibody ANGPTL3 inhibitor, may be a potential therapeutic option for patients with sHTG[4,6-8]
- In this Phase 2 study (NCT03452228), we evaluated the efficacy and safety of evinacumab in patients with sHTG who had ≥1 prior hospitalization for AP

ANGPTL3, angiopoietin-like 3; AP, acute pancreatitis; LOF, loss of function; TG, triglyceride.

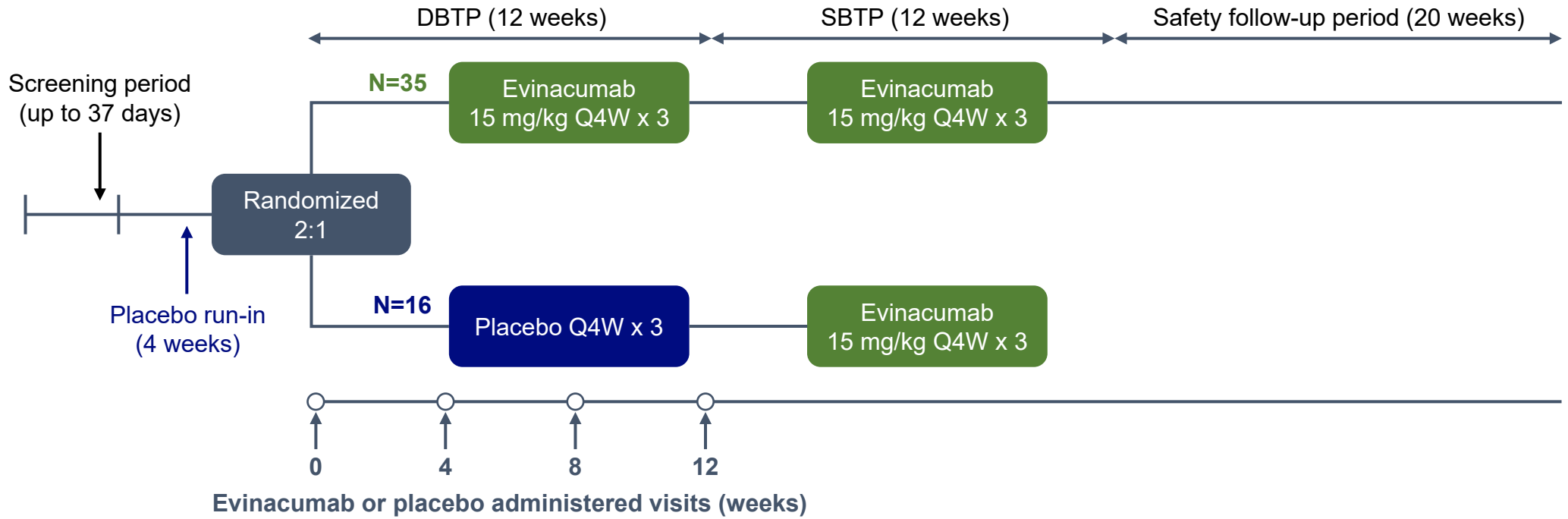
Methods

- In this double-blind, placebo-controlled, Phase 2 trial, 51 patients were treated and assigned to one of three cohorts based on genotype according to the presence of LOF mutations in LPL pathway genes
  - Aged 18–75 years
  - Presence of sHTG†
  - History of hospitalization for AP
- Patients were initially enrolled into their cohorts based on medical history at screening; however, they were subsequently genotyped by the Regeneron Genetics Center and reclassified into their actual cohort for the purpose of analysis

Actual Cohort	Mutation
1 (n=17)	Patients with FCS (with bi-allelic LOF mutations in *APOA5*, *APOC2*, *GPIHBP1*, *LMF1*, or *LPL*)
2 (n=15)	Patients with MCS (with known heterozygous LOF mutations in *APOA5*, *APOC2*, *GPIHBP1*, *LMF1*, or *LPL*)
3 (n=19)	Patients with MCS and without LPL pathway mutations

†Fasting serum TGs ≥500 mg/dL at screening on two separate occasions; medical history of fasting TGs ≥1000 mg/dL
AP, acute pancreatitis; FCS, familial chylomicronemia syndrome; LOF, loss of function; LPL, lipoprotein lipase; MCS, multifactorial chylomicronemia syndrome; sHTG, severe hypertriglyceridemia

Methods



- The primary endpoint was to determine the intra-patient change in serum TGs from baseline following 12 weeks of intravenous evinacumab treatment (combination of DBTP and SBTP) in Cohort 3 patients*

*Patients with MCS and without LPL pathway mutations
DBTP, double-blind treatment period; Q4W, every 4 weeks; SBTP, single-blind treatment period; TG, triglyceride.

Results

- Patient demographics and baseline characteristics were generally well balanced

	Actual Cohort 1		Actual Cohort 2		Actual Cohort 3	
	Placebo IV Q4W (n=5)	Evinacumab IV 15 mg/kg Q4W (n=12)	Placebo IV Q4W (n=6)	Evinacumab IV 15 mg/kg Q4W (n=9)	Placebo IV Q4W (n=5)	Evinacumab IV 15 mg/kg Q4W (n=14)
Age, years, mean (SD)	43.2 (15.7)	51.3 (9.4)	52.8 (13.5)	48.7 (10.3)	41.2 (7.8)	46.1 (11.0)
Male, n (%)	4 (80.0)	6 (50.0)	2 (33.3)	6 (66.7)	3 (60.0)	6 (42.9)
White, n (%)	4 (80.0)	11 (91.7)	5 (83.3)	7 (77.8)	3 (60.0)	11 (78.6)
BMI, kg/m^2, mean (SD)	26.6 (4.1)	26.8 (5.2)	27.9 (5.6)	31.5 (4.3)	30.0 (1.9)	28.9 (5.0)
History of AP, n (%)	5 (100)	12 (100)	6 (100)	9 (100)	5 (100)	14 (100)
Time from the most recent occurrence of AP, years, mean (SD)*	5.5 (7.8)	8.5 (9.6)	1.9 (1.1)	3.9 (3.8)	1.8 (1.6)	3.0 (4.6)
Concomitant LLT, n (%)	3 (60.0)	6 (50.0)	6 (100)	9 (100)	4 (80.0)	10 (71.4)
Baseline fasting TGs, mg/dL, median (Q1:Q3)	3918 (3122:3931)	3141 (2713:3921)	1352 (769:4010)	1238 (1020:2341)	1031 (1022:1496)	1917 (1196:2607)

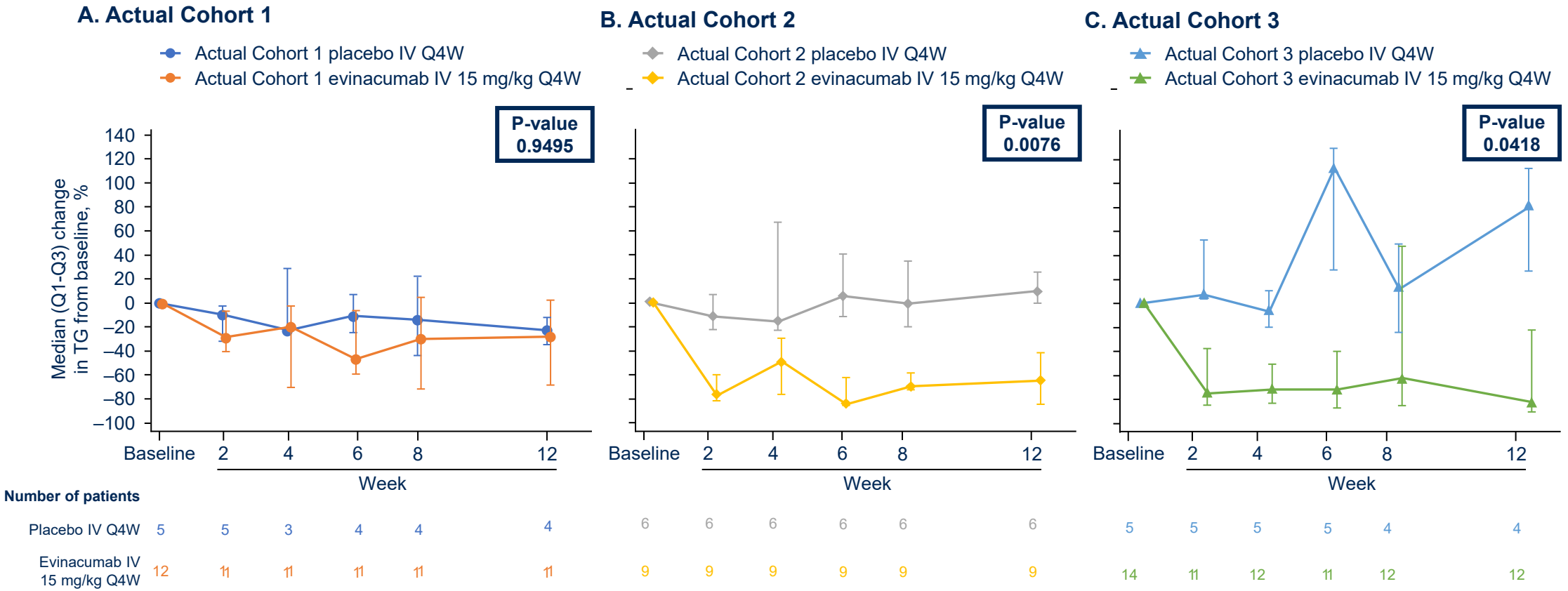
*Time from diagnosis to study randomization.
Cohort 1, patients with FCS (with bi-allelic LOF mutations in *APOA5, APOC2, GPIHBP1, LMF1*, or *LPL*); cohort 2, patients with MCS (with known heterozygous LOF mutations in *APOA5, APOC2, GPIHBP1, LMF1*, or *LPL*) ; cohort 3, patients with MCS and without LPL pathway mutations
AP, acute pancreatitis; BMI, body mass index; IV, intravenous; LLT, lipid-lowering therapy; Q4W, every 4 weeks; SD, standard deviation.

Results

- In cohort 3, the least squares mean (SE) reduction in TGs from baseline (pre-specified primary endpoint) was –27.1% (37.4%) 95% CI –71.2 to 84.6, and the corresponding median reduction in TGs was –68.8% (95% CI –84.1 to –38.8) (absolute median change in TG of –905 mg/dL from baseline), after 12 weeks of treatment (combination of DBTP and SBTP)
- Cohorts 2 and 3 showed clinically meaningful reductions in TGs during the DBTP. The median change in TG was –64.8% versus +9.4% for placebo in Cohort 2, and –81.7% versus +80.9% in Cohort 3
- Overall, changes in lipid/lipoprotein parameters observed during the DBTP were maintained during the SBTP for cohorts 2 and 3

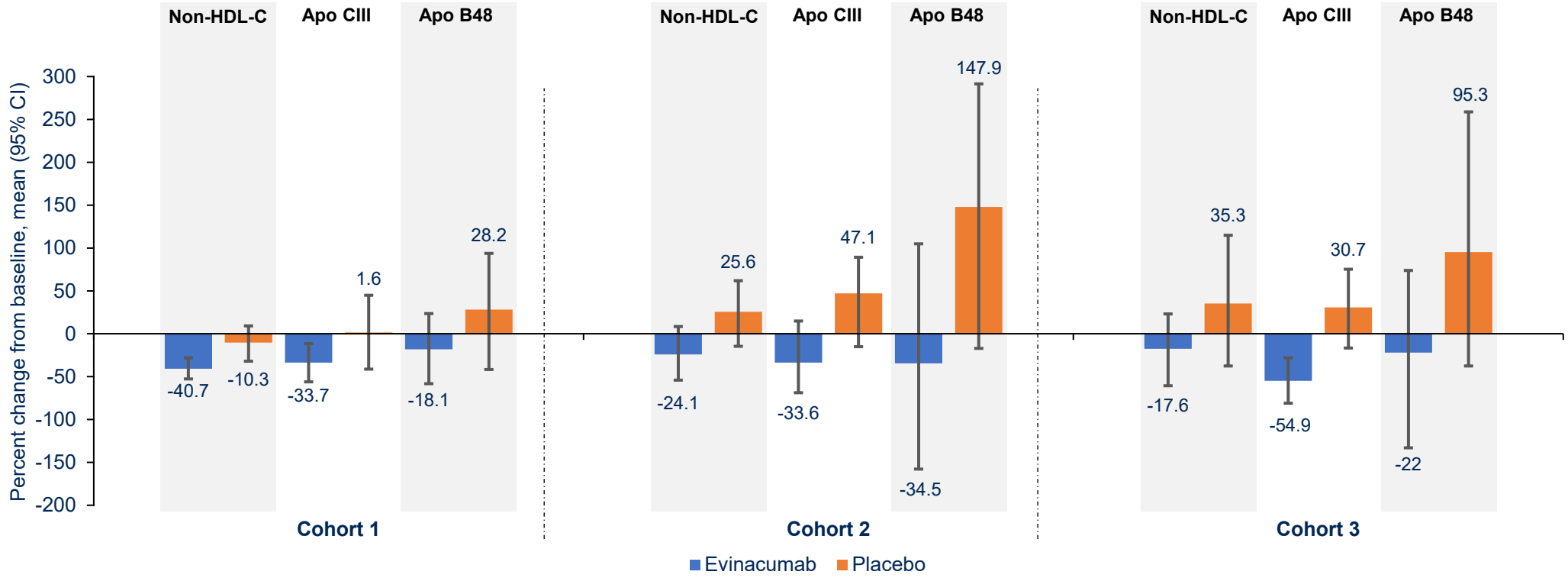
CI, confidence interval; DBTP, double-blind treatment period; SBTP, single-blind treatment period; SE, standard error; TG, triglyceride.

Results



IV, intravenous; Q4W, every 4 weeks; TG, triglyceride.

Results



- Substantial reductions in non-HDL-C, Apo CIII, Apo B48 were also observed from baseline to week 12

Nominally significant P-values for ApoC3, non-HDL-C and total ApoB overall for evinacumab vs. placebo.
Apo, apolipoprotein; CI, confidence interval; non-HDL-C, non-high-density lipoprotein cholesterol.

Results

- TEAEs occurred in a similar proportion of patients in the evinacumab and placebo groups during the SBTP, inclusive of the 20-week off-drug period
- Five AP events were reported by five patients during the DBTP (8.6% evinacumab group [n=3/35]; 12.5% placebo group [n=2/16])
- During the 12-week SBTP active treatment period, seven AP events were reported in five patients
- Most AP events occurred in the off-drug period >4 weeks after the last evinacumab dose, when TGs had increased towards pre-treatment levels and evinacumab concentrations had decreased to sub-therapeutic levels

AP, acute pancreatitis; DBTP, double-blind treatment period; IV, intravenous; Q4W, every 4 weeks; SBTP, single blind treatment period; TEAE, treatment-emergent adverse event; TG, triglyceride.

Results

TEAEs in >5% of patients* N (%) of patients	Placebo IV Q4W (N=16)	Evinacumab 15 mg/kg IV Q4W (N=35)
Patients with at least one TEAE	11 (68.8)	25 (71.4)
Patients with at least one serious TEAE	3 (18.8)	4 (11.4)
Patients with at least one TEAE resulting in discontinuation of treatment	0	2 (5.7)
Patients with at any TEAE resulting in death	0	0
TEAEs occurring in ≥2 patients in any group		
Abdominal pain	2 (12.5)	5 (14.3)
Headache	1 (6.3)	4 (11.4)
Constipation	0	3 (8.6)
Acute pancreatitis	2 (12.5)	3 (8.6)
Abdominal discomfort	0	2 (5.7)
Alanine aminotransferase increased	0	2 (5.7)
Aspartate aminotransferase increased	0	2 (5.7)
Back pain	0	2 (5.7)
Contusion	0	2 (5.7)
Dizziness	0	2 (5.7)
Herpes zoster	0	2 (5.7)
Nasopharyngitis	1 (6.3)	2 (5.7)
Sinusitis	0	2 (5.7)
Type 2 diabetes mellitus	1 (6.3)	2 (5.7)

*Occurring during the DBTP. AP, acute pancreatitis; DBTP, double-blind treatment period; IV, intravenous; Q4W, every 4 weeks; SBTP, single blind treatment period; TEAE, treatment-emergent adverse event; TG, triglyceride.

Conclusions

- In patients with sHTG, but without genetic FCS, evinacumab substantially reduced fasting TG levels; however, the treatment response was highly variable and dependent on genotype
- Data from this study supports further assessment of the effects of evinacumab in patients with sHTG, especially those with a history of sHTG-associated AP
- A Phase 2b trial will investigate the efficacy of TG lowering with evinacumab on the prevention of AP (NCT04863014)

AP, acute pancreatitis; sHTG, severe hypertriglyceridemia; TG, triglyceride.

Disclosures

- **RSR** reports grants and/or personal fees from Regeneron Pharmaceuticals, Inc., Amgen, The Medicines Company, Novartis, CVS Caremark, Kowa, UpToDate, and 89Bio; and reports stock holdings in MediMergent, LLC
- **DG** reports grants and/or personal fees from Akcea, Amryt Pharma, Arrowhead, Esperion, Gemphire, HDL Therapeutics, Novartis, Regeneron Pharmaceuticals, Inc., and Sanofi.
- **CMB** reports grants from Abbott Diagnostic, Akcea, Amarin, Amgen, Esperion, Ionis, Novartis, Regeneron Pharmaceuticals, Inc, Roche Diagnostic, and Sanofi-Synthelabo; and consultancy fees from Akcea, Amarin, Amgen, Arrowhead, Astra Zeneca, Boehringer Ingelheim, Denka Seiken, Esperion, Intercept, Janssen, Matinas BioPharma Inc, Merck, Novartis, Novo Nordisk, Regeneron Pharmaceuticals, Inc., and Sanofi-Synthelabo.
- **SJB** reports grants and/or personal fees from Akcea, Amgen, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Akcea, Amgen, Regeneron Pharmaceuticals, Inc., Sanofi, Novo Nordisk, Guidepoint Global, GLG Group, Akcea, Amgen, and Esperion.
- **JB** reports grants and/or personal fees from Akcea, Amgen, HLS Therapeutic, Inc., Kowa, Novartis, Regeneron Pharmaceuticals, Inc., and Sanofi.
- **EEK** reports grants and/or personal fees from Regeneron Pharmaceuticals, Inc.
- **PMM** reports consultancy/advisory board fees from Aegerion, Duke, Eliaz Therapeutics, Esperion, Gemphire Therapeutics, Kaneka, Kastle Therapeutics, RegenXBio, and Stage 2 Innovations; speaker fees from Amarin, Ambry Genetics, Amgen, Regeneron Pharmaceuticals, Inc., and Sanofi; and research funding from Akcea, Amgen, FH Foundation, Gemphire, Ionis, Kaneka, Kowa, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sanofi, Stage 2 Innovations, University of Pennsylvania, and Zydus Discovery.
- **PR** reports grants from Regeneron Pharmaceuticals, Inc.
- **DCW** has been a consultant to AbbVie, Abbott, Ariel Precision Medicine, BioNTech, Nestle, Novartis, Regeneron, Samsung, Takata, is a co-founder and of Ariel Precision Medicine and may have equity and reports personal fees as Section Editor, Pancreas for UpToDate and as Editor-in-Chief of Clinical and Transitional Gastroenterology. PB, MP, RP, and VS are employees and/or stockholders of Regeneron Pharmaceuticals, Inc.
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Funding

- This study was funded by Regeneron Pharmaceuticals, Inc.

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