Pegozafermin Provides Beneficial Lipid Effects in Subjects with Severe Hypertriglyceridemia (SHTG) Regardless of Background Lipid Modifying Therapy Status: An Analysis of the Phase 2 ENTRIGUE study

Deepak L. Bhatt, MD, MPH; Harold E. Bays, MD; Michael Miller, MD, FACC, FAHA; Teresa Parli, MD; Shibao Feng, PhD, Lulu Sterling, PhD; Cynthia L. Hartsfield, PhD; Germaine D. Agollah, PhD; Hank Mansbach, MD; John J. P. Kastelein, MD, PhD, on Behalf of the ENTRIGUE Investigators

ENtrigue

INTRODUCTION

- Fibroblast growth factor 21 (FGF21) is an endogenous hormone-regulating lipid and glucose metabolism and energy expenditure.
- Pegozafermin (PGZ) is a glycoPEGylated FGF21 analog designed to have a longer half-life than native FGF21.
- PGZ is currently being developed for treatment of severe hypertriglyceridemia (SHTG) and non-alcoholic steatohepatitis (NASH).
- Data from a phase 1b/2a POC study in subjects with NASH demonstrated overall metabolic benefit with improvements in lipids (TG, LDL, non-HDL and HDL), insulin resistance, HbA1c, body weight, and liver fat.

BACKGROUND

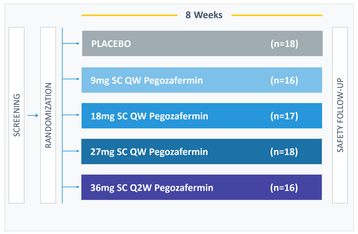
- Severe hypertriglyceridemia (SHTG; ≥500mg/dL) increases the risk of acute pancreatitis and cardiovascular disease.
- Current therapies often do not reduce TG levels to desired levels, highlighting the need for new therapeutic options.
- SHTG is commonly associated with obesity, metabolic syndrome, insulin resistance, type 2 diabetes mellitus and non-alcoholic fatty liver disease (NAFLD).
- An ideal therapy would not only lower TG levels but also provide benefit for other metabolic comorbidities.

OBJECTIVE

- This sub-analysis of the ENTRIGUE trial was designed to investigate if background lipid modifying therapy (LMT) impacted the efficacy of PGZ as a novel therapeutic agent for the treatment of SHTG.

METHODS

Randomized, Double-Blind, Phase 2 Trial of Subjects with Severe Hypertriglyceridemia (ENTRIGUE)



KEY INCLUSION CRITERIA

- TG ≥500 mg/dL and ≤2,000 mg/dL
- Background therapy: statins and/or prescription omega-3 fatty acids, and/or fibrates OR none
- Randomization was stratified by background therapy (Y/N)

PRIMARY ENDPOINT

- Primary endpoint: % Change in TGs from baseline

KEY SECONDARY ENDPOINTS

- Lipids: non-HDL-C, HDL-C, Apo-B
- Liver fat (MRI-PDFF)
- Glycemic control

Magnetic Resonance Imaging – Proton Density Fat Fraction.
SQ, subcutaneously; QW, once-weekly; Q2W, once every two weeks.

Safety analysis set, n=85 (patients who received at least 1 dose).
Full analysis set, n=82 (patients with at least 1 post-baseline TG assessment).
MRI analysis set n=23 (patients with baseline and end of treatment MRIs).

RESULTS

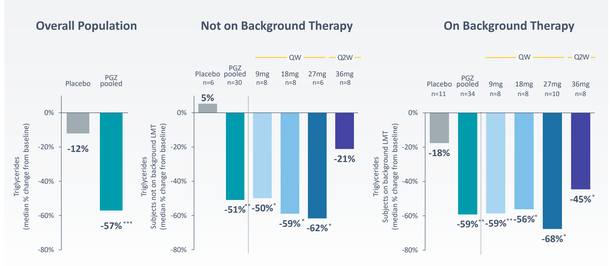
Baseline Characteristics

Represents a population at high risk for cardiovascular disease

Parameter Mean or %	Placebo (n=18)	PGZ Pooled (n=67)	PGZ 9mg QW (n=16)	PGZ 18mg QW (n=17)	PGZ 27mg QW (n=18)	PGZ 36mg Q2W (n=16)	Total (n=85)
Age (years)	57.5	52.7	54.6	49.2	53.9	53.1	**53.7**
Male (%)	66.7	77.6	68.8	82.4	72.2	87.5	**75.3**
BMI (kg/m^2)	33.1	33.1	32.9	32.3	34.2	32.9	**33.1**
Type 2 diabetes (%)	61.1	47.8	56.3	35.3	55.6	43.8	**50.6**
TG (mg/dL)	720	736	722	709	680	840	**733**
Non-HDL-C (mg/dL)	220	209	216	203	203	215	**211**
HDL-C (mg/dL)	28	28	31	27	31	25	**28**
LDL-C (mg/dL)	88	89	92	88	97	80	**89**
Apo-B (mg/dL)	116	115	120	115	119	106	**115**
Any background therapy	61.1%	53.7%	50.0%	52.9%	61.1%	50.0%	**55.3%**
Statins/statin combo	50%	43%	38%	53%	39%	44%	**45%**
Omega-3 fatty acids/ omega 3s	11%	15%	6%	12%	22%	19%	**14%**
Fibrates	17%	5%	0	0	17%	0	**7.1%**
Other	6%	13%	13%	18%	11%	13%	**12%**
Liver Fat Content (%) (n=24)	16.5 [n=6]	21.3 [n=18]	19.8 [n=3]	18.0 [n=5]	22.4 [n=7]	25.5 [n=3]	**20.1 [n=24]**

Patients may be on > 1 lipid-modifying therapy.
Background therapy defined as concomitant lipid-modifying therapy.
Other includes bempedoic acid, ezetimibe alone, and ezetimibe as ingredient in combination.

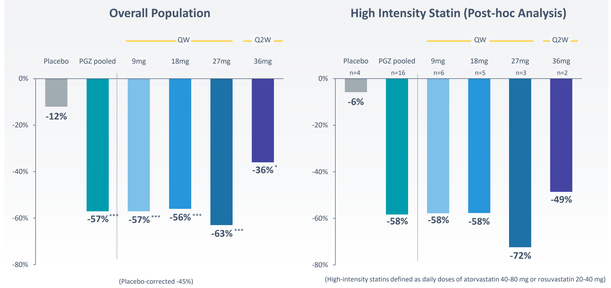
Primary Endpoint: Triglyceride Reduction



P value vs placebo for change from baseline based on van Elteren Test for pooled PGZ and Wilcoxon Rank-Sum Test for individual PGZ groups.
Full Analysis Set; *p<0.05; **p<0.01; ***p<0.001 versus placebo versus placebo.

QW: Every week; Q2W: Every 2 weeks.

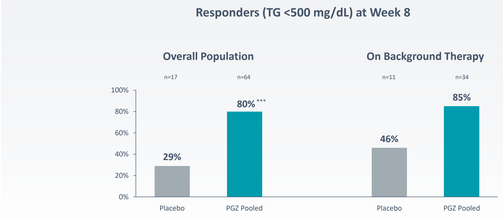
PGZ Led to Reductions in Triglycerides Among Subjects on Background High Intensity Statins



P value vs placebo for change from baseline based on van Elteren Test for pooled PGZ and Wilcoxon Rank-Sum Test for individual PGZ groups.
Full Analysis Set; *p<0.05; **p<0.01; ***p<0.001 versus placebo versus placebo.

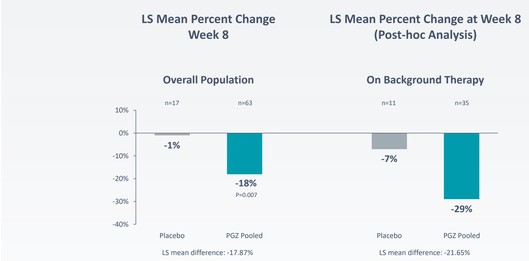
QW: Every week; Q2W: Every 2 weeks.

PGZ Treated Subjects Reach Initial Treatment Goal



P value vs placebo for change from baseline based on Cochran Mantel-Haenszel Test for pooled PGZ and Wilcoxon Rank-Sum Test for individual PGZ groups.
Full Analysis Set; *p<0.05; **p<0.01; ***p<0.001 versus placebo versus placebo.

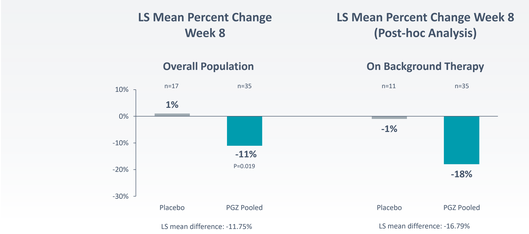
PGZ Led to Improvements in Non-HDL Cholesterol



Results are consistent with data from subjects on background therapy of statins or statin combos, prescription omega-3s, and fibrates

Least squares means data based on MMRM analysis.
Full Analysis Set.

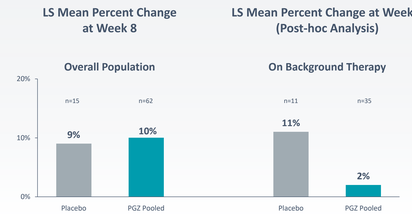
PGZ Led to Improvements in Apolipoprotein B



Results are consistent with data from subjects on background therapy of statins or statin combos, prescription omega-3s, and fibrates

Least squares means data based on MMRM analysis.
Full Analysis Set.

No Significant Changes in LDL Cholesterol



Results are consistent with data from subjects on background therapy of statins or statin combos, prescription omega-3s, and fibrates

Least squares means data based on MMRM analysis.
Full Analysis Set.

Safety: PGZ Was Well Tolerated Across Doses

Low incidence of treatment-related AEs in ≥ 7.5% of pooled PGZ group

	Placebo (n=18)	PGZ Pooled (n=67)	PGZ 9mg QW (n=12)	PGZ 18mg QW (n=21)	PGZ 27mg QW (n=18)	PGZ 36mg Q2W (n=16)
Nausea	0	10%	0%	5%	22%	13%
Diarrhea	0	9%	17%	5%	17%	13%
Injection-site reaction	0	9%	8%	10%	6%	13%

All AEs were grade 1 or 2; No grade 3 or higher TEAEs reported. No transaminase elevation AEs reported

	Placebo (n=18)	PGZ Pooled (n=67)	PGZ 9mg QW (n=12)	PGZ 18mg QW (n=21)	PGZ 27mg QW (n=18)	PGZ 36mg Q2W (n=16)
Serious adverse event (unrelated)	0	1*	0	0	1	0
Treatment emergent discontinuations (related/unrelated)	0	2^/2	0	0	2^/2	0

*Unrelated SAE of grade 2 hypertension; patient withdrew.
^Grade 2 abdominal cramps (1) and Grade 2 nausea/vomiting (1).
Safety Analysis Set; patients reported on as treated basis.

CONCLUSIONS

- PGZ significantly reduced TG and other atherogenic lipids in subjects with SHTG.
- These results remained consistent in subjects on background lipid modifying therapy whether statin, statin combination, prescription omega-3 fatty acids, or fibrates.
- Findings are limited by the small sample size of the trial.
- Previous data have demonstrated PGZ provides additional cardiometabolic improvements (such as glycemic regulation and liver fat reduction).
- PGZ is an attractive therapy for the treatment of SHTG with the potential to address multiple comorbidities simultaneously, including cardiac, glycemic, and hepatic risks.
- These data appear very promising for the planned phase 3 trial utilizing the higher weekly dose(s) given for a longer duration.