Pegozafermin for the Treatment of Severe Hypertriglyceridemia: A Randomized, Double-blind, Placebo-controlled Phase 2 Study (ENTRIGUE STUDY)

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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

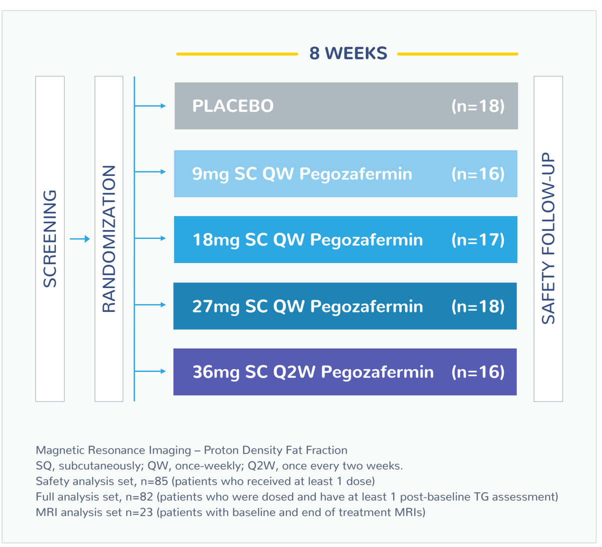
- SHTG ≥500mg/dL increases the risk of acute pancreatitis and cardiovascular disease.
- Current approved therapies reduce TG levels, however many SHTG patients do not attain desired levels (TG levels <500 mg/dl) leaving residual risk for acute pancreatitis and highlighting the need for new therapeutic options.
- SHTG is commonly associated with obesity, metabolic syndrome, insulin resistance, type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD).
- An ideal therapy would not only lower TG levels, but provide benefit for other metabolic comorbidities.

OBJECTIVE

- The ENTRIGUE trial was designed to investigate PGZ as a novel therapeutic agent for the treatment of SHTG

METHODS

Randomized, Double-Blind, Phase 2 Trial of Patients with SHTG (ENTRIGUE)


8 WEEKS
SCREENING
RANDOMIZATION
PLACEBO (n=18)
9mg SC QW Pegozafermin (n=16)
18mg SC QW Pegozafermin (n=17)
27mg SC QW Pegozafermin (n=18)
36mg SC Q2W Pegozafermin (n=16)
SAFETY FOLLOW-UP

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 who were dosed and have at least 1 post-baseline TG assessment)
MRI analysis set n=23 (patients with baseline and end of treatment MRIs)

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

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

RESULTS

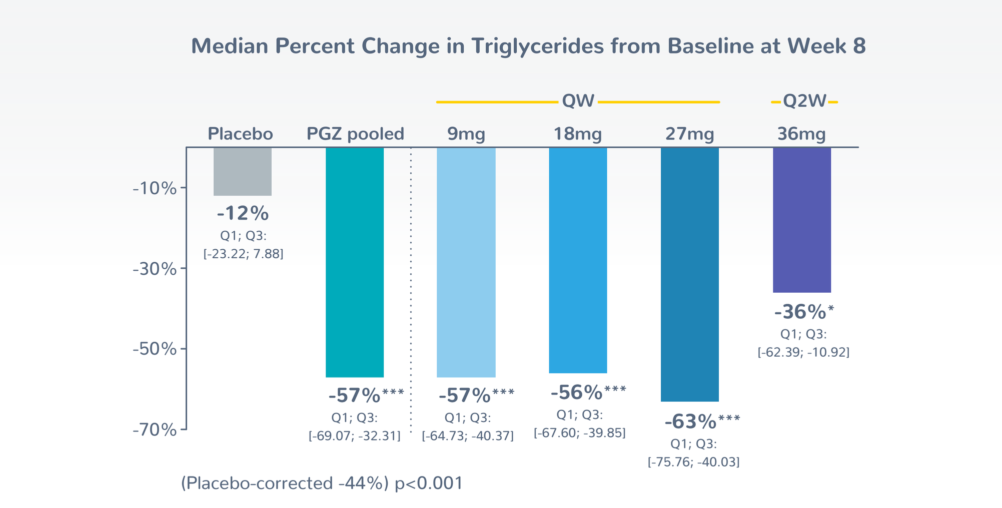
Baseline Characteristics

Represents a population at high risk for cardiovascular disease

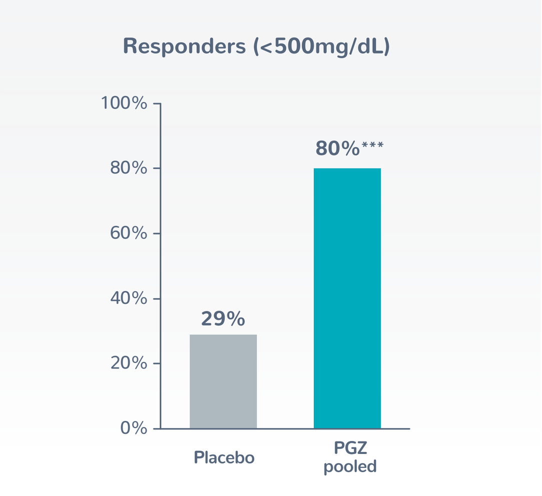
Parameter Mean or %	Placebo (n=18)	PGZ Pooled (n=67)	PGZ 9mg QW (n=16)	PGZ 18mg QW (n=17)	PGZ 27mg QW (n=18)	PGZ 36mg Q2W (n=16)	Total (n=85)
Age (years)	57.5	52.7	54.6	49.2	53.9	53.1	53.7
Male (%)	66.7	77.6	68.8	82.4	72.2	87.5	75.3
BMI (kg/m²)	33.1	33.1	32.9	32.3	34.2	32.9	33.1
Type 2 Diabetes (%)	61.1	47.8	56.3	35.3	55.6	43.8	50.6
Triglyceride (mg/dL)	720.3	735.8	721.7	709.5	680.3	840.3	732.5
non-HDL cholesterol (mg/dL)	219.6	209.3	216.2	203.2	203.4	215.4	211.5
HDL cholesterol (mg/dL)	28.3	28.4	30.7	27.3	30.6	24.8	28.4
LDL cholesterol (mg/dL)	87.9	89.4	91.6	88.3	97.3	79.5	89.1
Apolipoprotein B (ApoB) (mg/dL)	116.3	115.3	120.1	115.3	119.3	105.9	115.5
HbA1c ≥6.5%, n (%)	7 (38.9)	30 (44.8)	9 (56.3)	6 (35.3)	9 (50.0)	6 (37.5)	37 (43.5)
ALT (U/L)	29.1	33.9	36.3	36.9	33.0	29.2	32.8
Any background lipid-modifying therapy (LMT), n (%)	11 (61.1)	36 (53.7)	8 (50.0)	9 (52.9)	11 (61.1)	8 (50.0)	47 (55.3)
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]

PGZ Significantly Reduces Triglycerides Across All Dose Groups

Primary endpoint

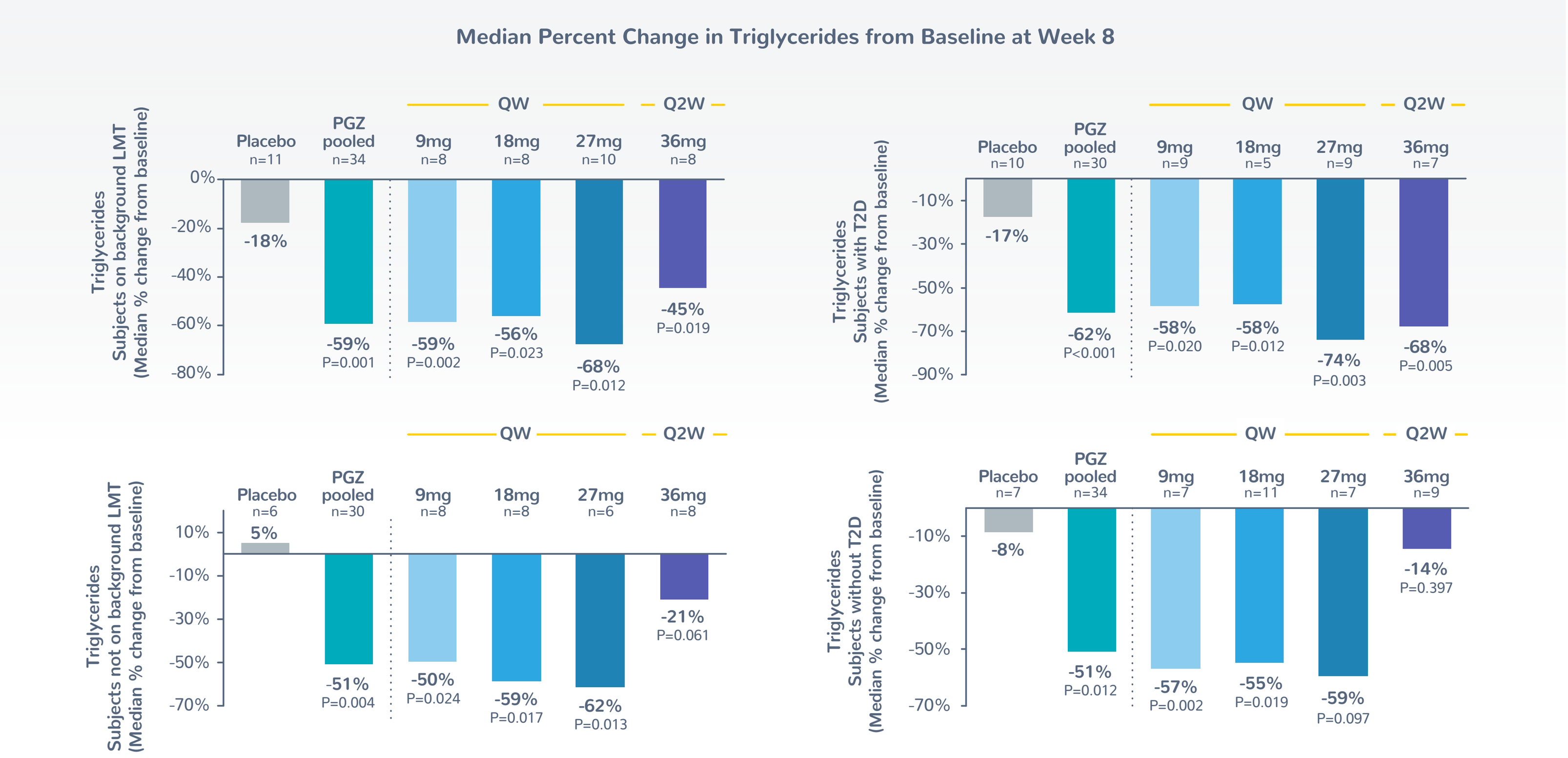

Median Percent Change in Triglycerides from Baseline at Week 8
QW
Q2W
Placebo
PGZ pooled
9mg
18mg
27mg
36mg
-12%
Q1; Q3: [-23.22; 7.88]
-57%***
Q1; Q3: [-69.07; -32.31]
-57%***
Q1; Q3: [-64.73; -40.37]
-56%***
Q1; Q3: [-67.60; -39.85]
-63%***
Q1; Q3: [-75.76; -40.03]
-36%*
Q1; Q3: [-62.39; -10.92]
(Placebo-corrected -44%) p<0.001

QW: Every week; Q2W: Every 2 weeks
Van Elteren Test for pooled PGZ; Wilcoxon Rank Sum for individual PGZ groups
Full Analysis Set; * p<0.05; *** p<0.001 versus placebo

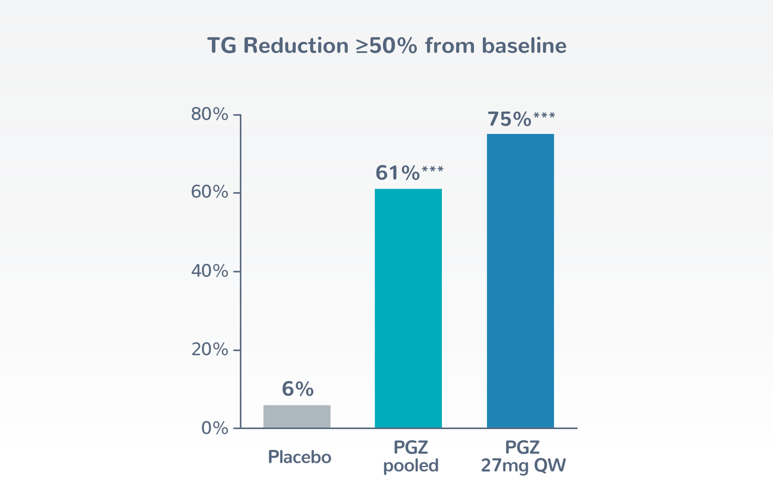

Responders (<500mg/dL)
29%
80%***
Placebo
PGZ pooled

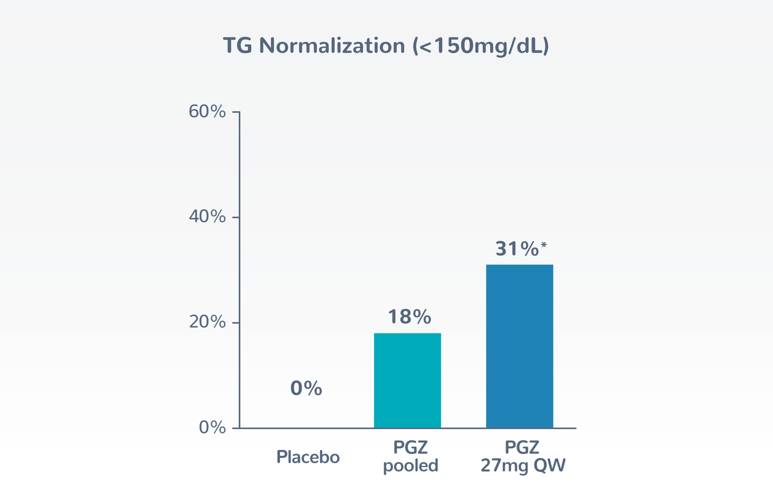
Analysis via Chi-square test comparing PGZ vs placebo
Full Analysis Set; * p<0.05; ** p<0.01; *** p<0.001
TG Responders defined as patients who achieve TG <500 mg/dL

PGZ Treatment Led to a Significant Reduction in Triglycerides Independent of Background LMT or T2DM Status


Median Percent Change in Triglycerides from Baseline at Week 8
Triglycerides Subjects on background LMT (Median % change from baseline)
Placebo n=11: -18%
PGZ pooled n=34: -59% P=0.001
9mg n=8: -59% P=0.002
18mg n=8: -56% P=0.023
27mg n=10: -68% P=0.012
36mg n=8: -45% P=0.019
Triglycerides Subjects not on background LMT (Median % change from baseline)
Placebo n=6: 5%
PGZ pooled n=30: -51% P=0.004
9mg n=8: -50% P=0.024
18mg n=5: -59% P=0.017
27mg n=6: -62% P=0.013
36mg n=8: -21% P=0.061
Triglycerides Subjects with T2D (Median % change from baseline)
Placebo n=10: -17%
PGZ pooled n=30: -62% P<0.001
9mg n=9: -58% P=0.020
18mg n=5: -58% P=0.012
27mg n=9: -74% P=0.003
36mg n=7: -68% P=0.005
Triglycerides Subjects without T2D (Median % change from baseline)
Placebo n=7: -8%
PGZ pooled n=34: -51% P=0.012
9mg n=7: -57% P=0.002
18mg n=11: -55% P=0.019
27mg n=7: -59% P=0.097
36mg n=9: -14% P=0.397

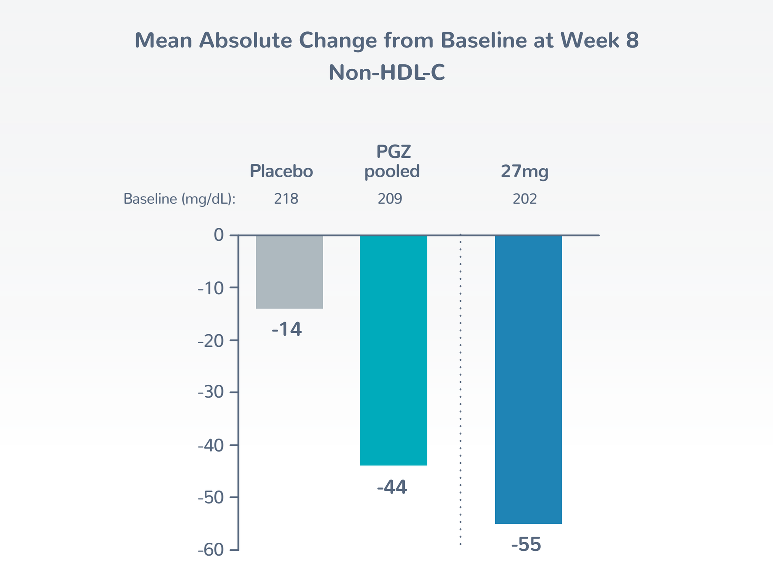
PGZ Significantly Decreases Triglycerides Across Various Threshold Levels

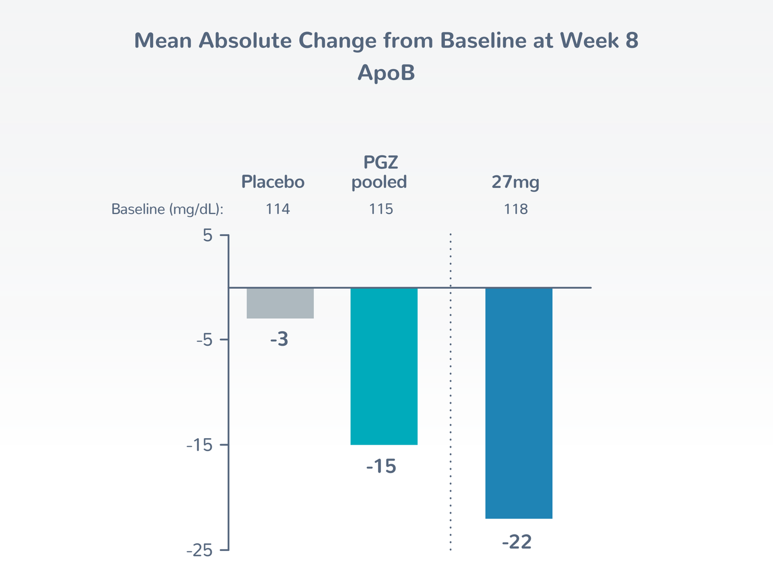

TG Reduction ≥50% from baseline
6%
61%***
75%***
Placebo
PGZ pooled
PGZ 27mg QW


TG Normalization (<150mg/dL)
0%
18%
31%*
Placebo
PGZ pooled
PGZ 27mg QW

Analysis via CMH and Chi-square test comparing the pooled and individual PGZ groups vs placebo respectively
Full Analysis Set; * p<0.05; ** p<0.01; *** p<0.001

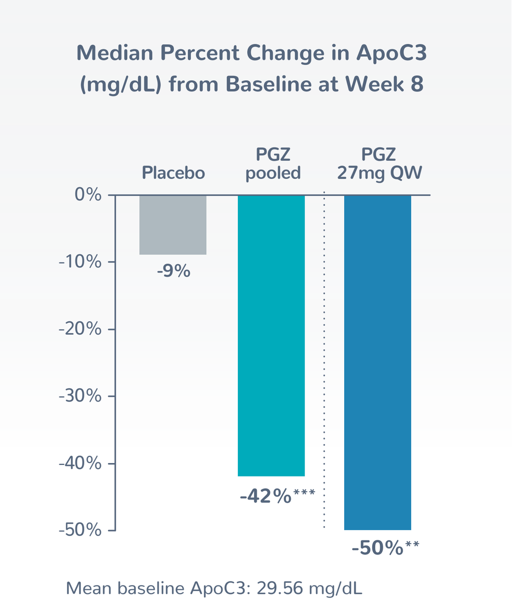
PGZ Demonstrated Reduction in Atherogenic Lipid Particles (Non-HDL-C and ApoB)


Mean Absolute Change from Baseline at Week 8
Non-HDL-C
Baseline (mg/dL):
Placebo 218: -14
PGZ pooled 209: -44
27mg 202: -55

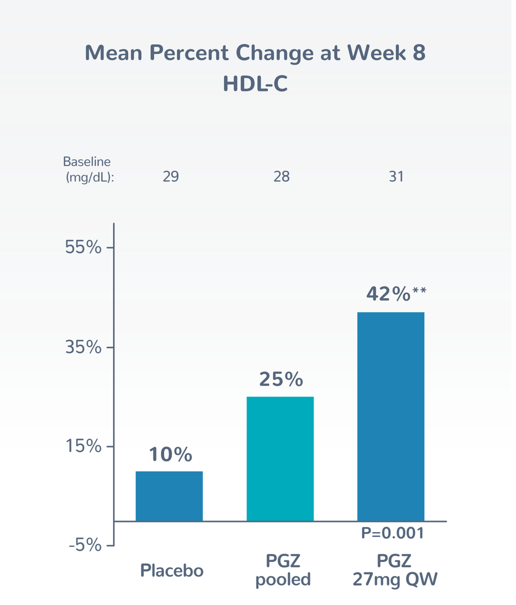

Mean Absolute Change from Baseline at Week 8
ApoB
Baseline (mg/dL):
Placebo 114: -3
PGZ pooled 115: -15
27mg 118: -22

Descriptive analysis was performed for mean absolute change

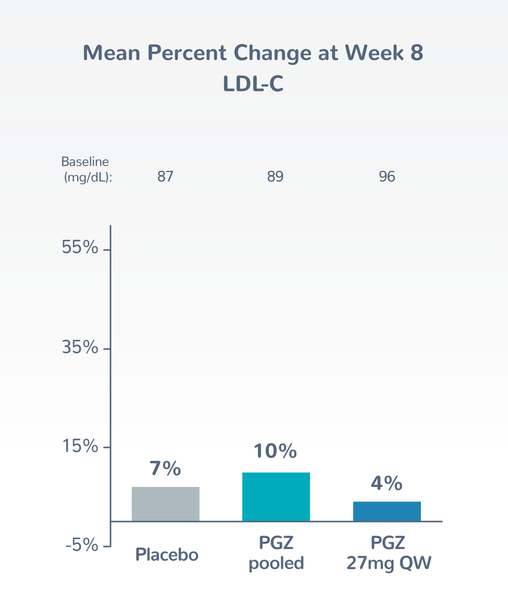
PGZ Decreases ApoC3 and Increases HDL-C with Minimal Impact on LDL-C


Median Percent Change in ApoC3 (mg/dL) from Baseline at Week 8
Placebo: -9%
PGZ pooled: -42%***
PGZ 27mg QW: -50%**
Mean baseline ApoC3: 29.56 mg/dL

Full Analysis Set; ** p<0.01; *** p<0.001; Van Elteren Test for pooled PGZ; Wilcoxon Rank-sum for individual PGZ groups

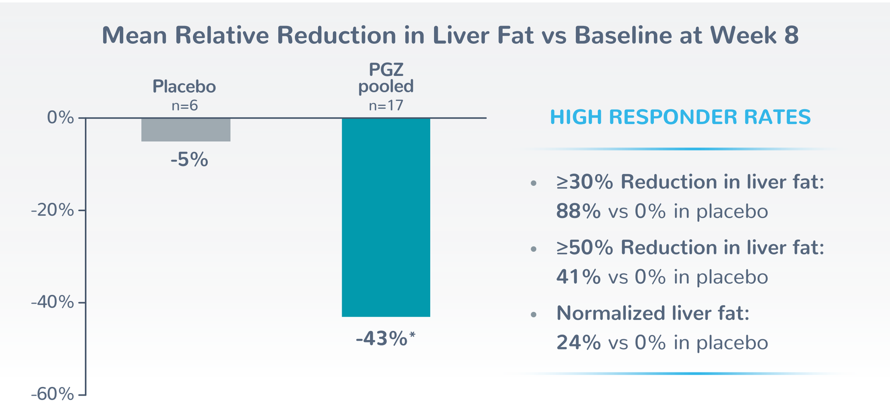

Mean Percent Change at Week 8
HDL-C
Baseline (mg/dL): 29 28 31
Placebo: 10%
PGZ pooled: 25%
PGZ 27mg QW: 42%**
P=0.001

Full Analysis Set; ** p=0.01 versus placebo based on MMRM analysis

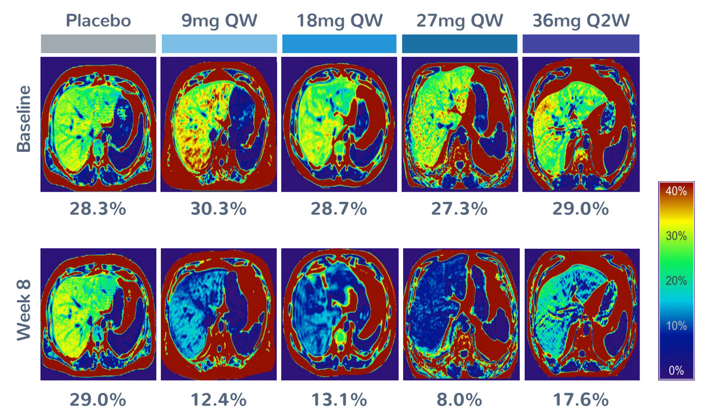

Mean Percent Change at Week 8
LDL-C
Baseline (mg/dL): 87 89 96
Placebo: 7%
PGZ pooled: 10%
PGZ 27mg QW: 4%

PGZ Demonstrated Significant Reduction in Liver Fat

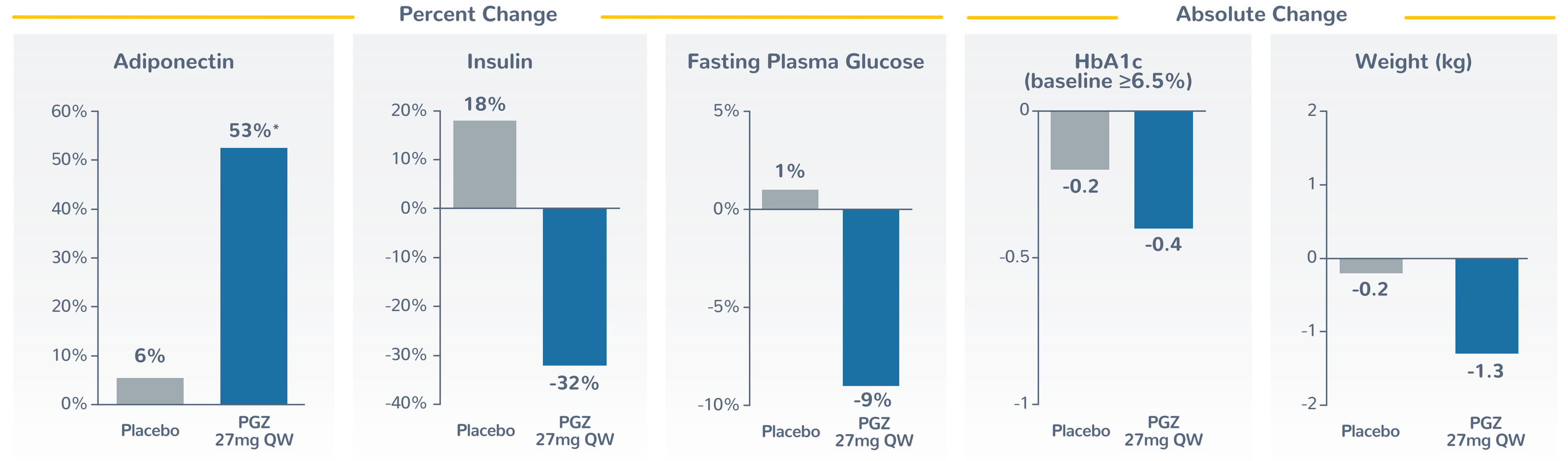
Liver fat is an important potentiator of cardiovascular risk


Mean Relative Reduction in Liver Fat vs Baseline at Week 8
Placebo n=6: -5%
PGZ pooled n=17: -43%*
HIGH RESPONDER RATES
≥30% Reduction in liver fat: 88% vs 0% in placebo
≥50% Reduction in liver fat: 41% vs 0% in placebo
Normalized liver fat: 24% vs 0% in placebo

MRI Analysis Set; p value vs placebo based on ANCOVA analysis
*p <0.05 vs placebo


Placebo
9mg QW
18mg QW
27mg QW
36mg Q2W
Baseline
28.3%
30.3%
28.7%
27.3%
29.0%
Week 8
29.0%
12.4%
13.1%
8.0%
17.6%

Higher Dose of PGZ Improves Markers of Insulin Sensitivity


Percent Change
Absolute Change
Adiponectin: Placebo 6%; PGZ 27mg QW 53%*
Insulin: Placebo 18%; PGZ 27mg QW -32%
Fasting Plasma Glucose: Placebo 1%; PGZ 27mg QW -9%
HbA1c (baseline ≥6.5%): Placebo -0.2; PGZ 27mg QW -0.4
Weight (kg): Placebo -0.2; PGZ 27mg QW -1.3

Full Analysis Set; Descriptive analysis
Mean Changes at Week 8; *p=0.017

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=16)	PGZ 18mg QW (n=17)	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=16)	PGZ 18mg QW (n=17)	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 in a subject with undiagnosed, uncontrolled hypertension at baseline; 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:
 - Triglycerides by ˜50-60%
 - Non-HDL-Cholesterol by ˜20-30%
 - ApoB by ˜10-20%
 - Liver fat fraction by ˜40%
- Additional cardiometabolic improvements potentially make pegozafermin an attractive therapy in SHTG to address multiple co-morbidities 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.
- A randomized double-blind placebo-controlled phase 2b study in NASH is fully enrolled with data expected in 1Q23 (NCT04929483).

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