ENtrigue

Phase 2 Trial of Pegozafermin in Severe Hypertriglyceridemia

Deepak L. Bhatt, MD, MPH; Harold E. Bays, MD; Michael Miller, MD, FACC, FAHA; James E. Cain III, MD; Katarzyna Wasilewska, MD; Nabil S. Andrawis, MD, PhD, FACP; Teresa Parli, MD; Shibao Feng, PhD, Lulu Sterliing, PhD; Cynthia L. Hartsfield, PhD; Germaine D. Agollah, PhD; Hank Mansbach, MD; John J. P. Kastelein, MD, PhD, on Behalf of the ENTRIGUE Investigators

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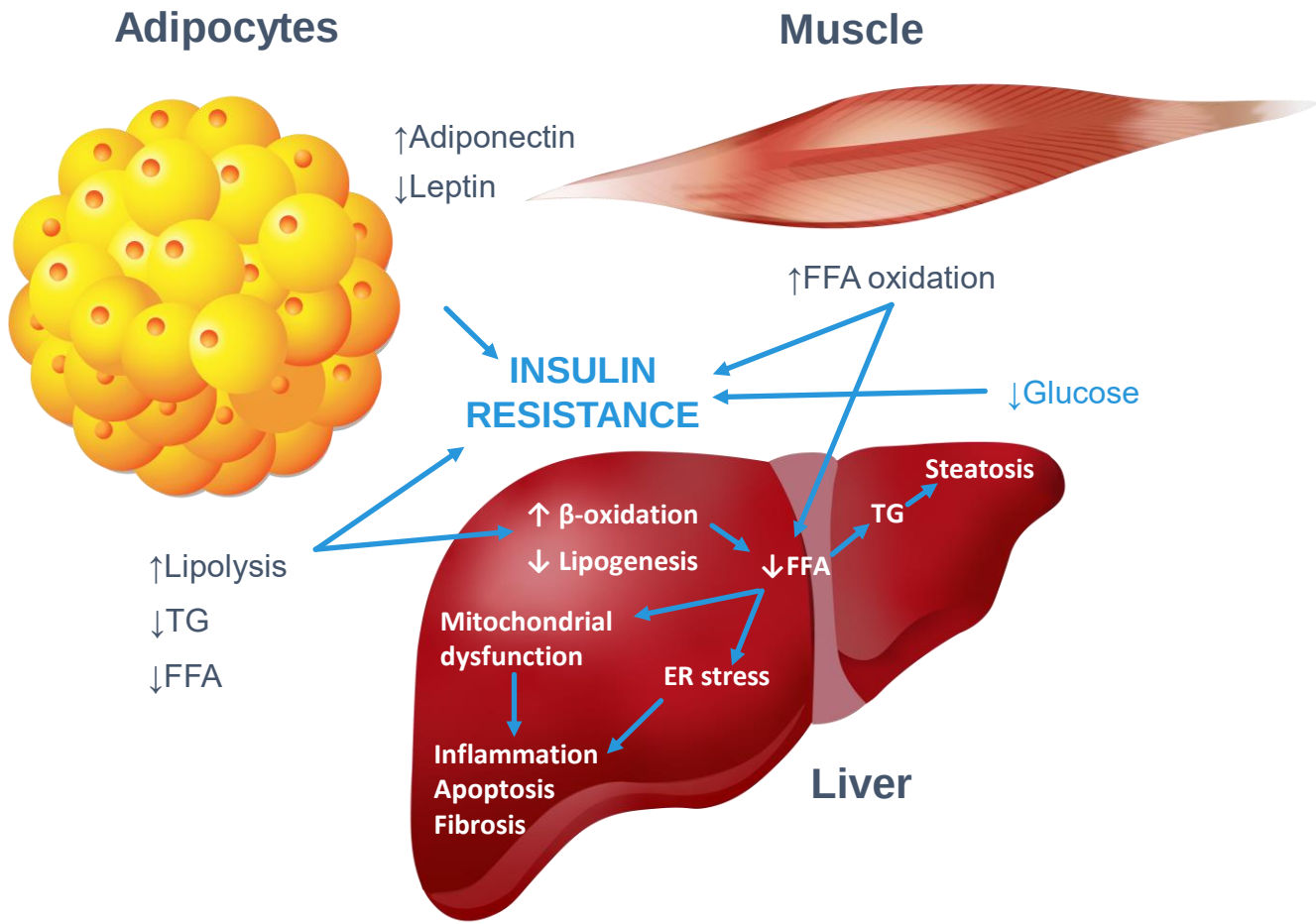
This trial was sponsored by 89bio.
Dr. Bhatt receives research funding from 89bio paid to Brigham and Women's Hospital.

FGF21, an Endogenous Stress Hormone, Plays a Major Role in Regulating Lipid and Glucose Metabolism and Energy Expenditure

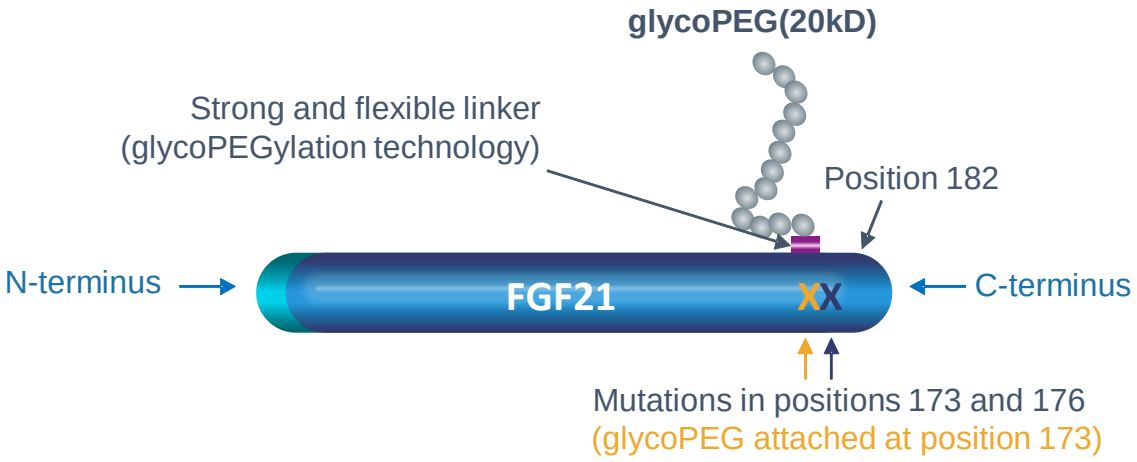
Proposed Mechanisms of Action for FGF21 in Severe Hypertriglyceridemia

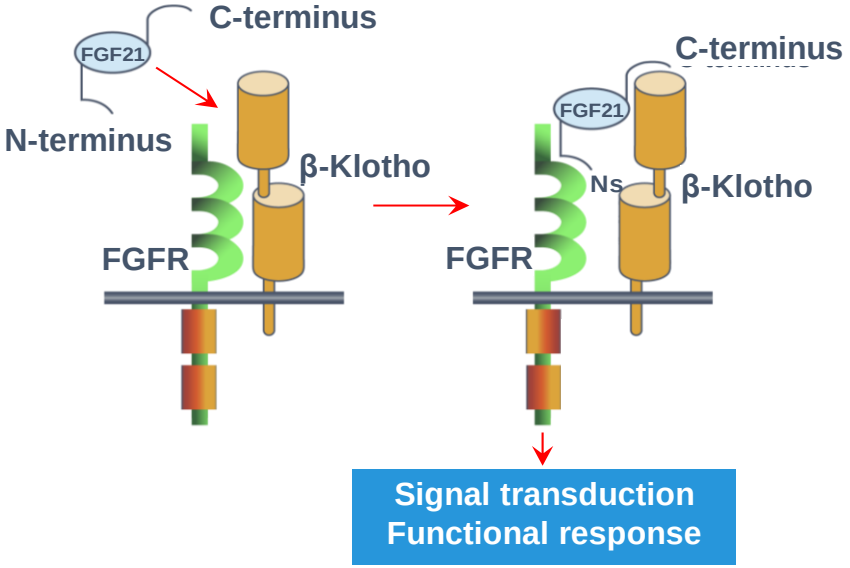
- **Adipose tissue**
  - Decrease lipogenesis and release of FFA
  - Improve insulin resistance
  - Increase TG uptake
  - Increase adiponectin
- **Liver**
  - Increase β-oxidation
  - Decrease de novo lipogenesis
  - Decrease FFA / TG
- **Muscle**
  - Increase FFA oxidation



Stojsavljevic-Shapeski S et al *J Clin Transl Hepatol* 2021;9(1):51-59

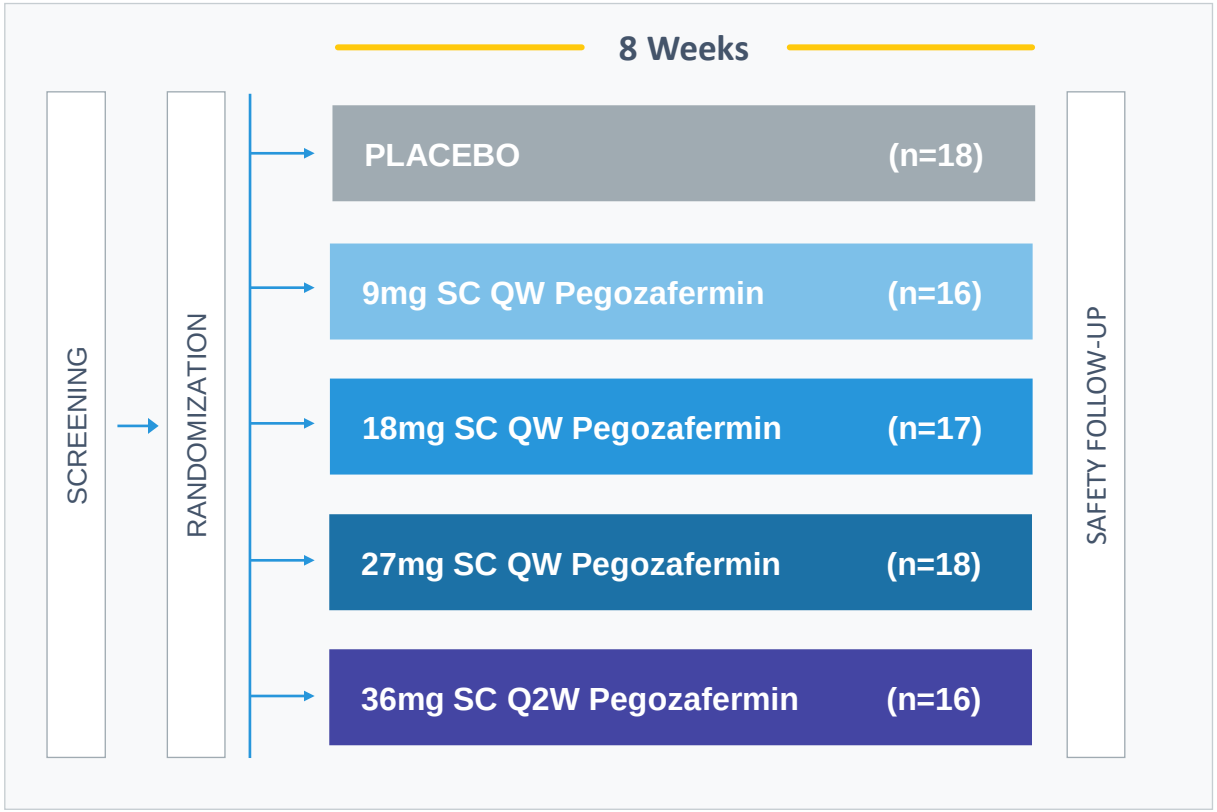
Pegozafermin is an FGF21 Analog Optimally Engineered for Efficacy with a Long Dosing Interval





- Using glycoPEGylation technology with site-specific mutations
- Increases half-life of native FGF21 (< 2 hours) to 55-100 hours based on single ascending dose study
- Low nanomolar potency against FGF receptors 1c, 2c, 3c, similar to native FGF21

ENTRIGUE – Randomized, Double-Blind, Phase 2 Trial of Patients with Severe Hypertriglyceridemia



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)

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

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**
HbA1c ≥6.5% (%)	38.9	44.8	56.3	35.3	50.0	37.5	**43.5**
ALT (U/L)	29.1	33.9	36.3	36.9	33.0	29.2	**32.8**
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]**

Baseline Characteristics: ~ 50% on Background Therapy

Consistent with a real-world setting

	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)
Any background therapy	61%	54%	50%	53%	61%	50%	**55%**
Statin*	50%	43%	38%	53%	39%	44%	**45%**
Prescription omega-3	11%	15%	6%	12%	22%	19%	**14%**
Fibrate	17%	5%	0	0	17%	0	**7%**
Other	6%	13%	13%	18%	11%	13%	**12%**

Patients may be on >1 lipid-modifying therapy
Background therapy defined as concomitant lipid-modifying therapy
*55% of statin use was high-intensity statin

Other includes bempedoic acid, ezetimibe alone and ezetimibe as ingredient in combination

Pegozafermin Was Well Tolerated Across Doses

Low incidence of treatment-related AEs in ≥ 7.5% of pooled pegozafermin 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.

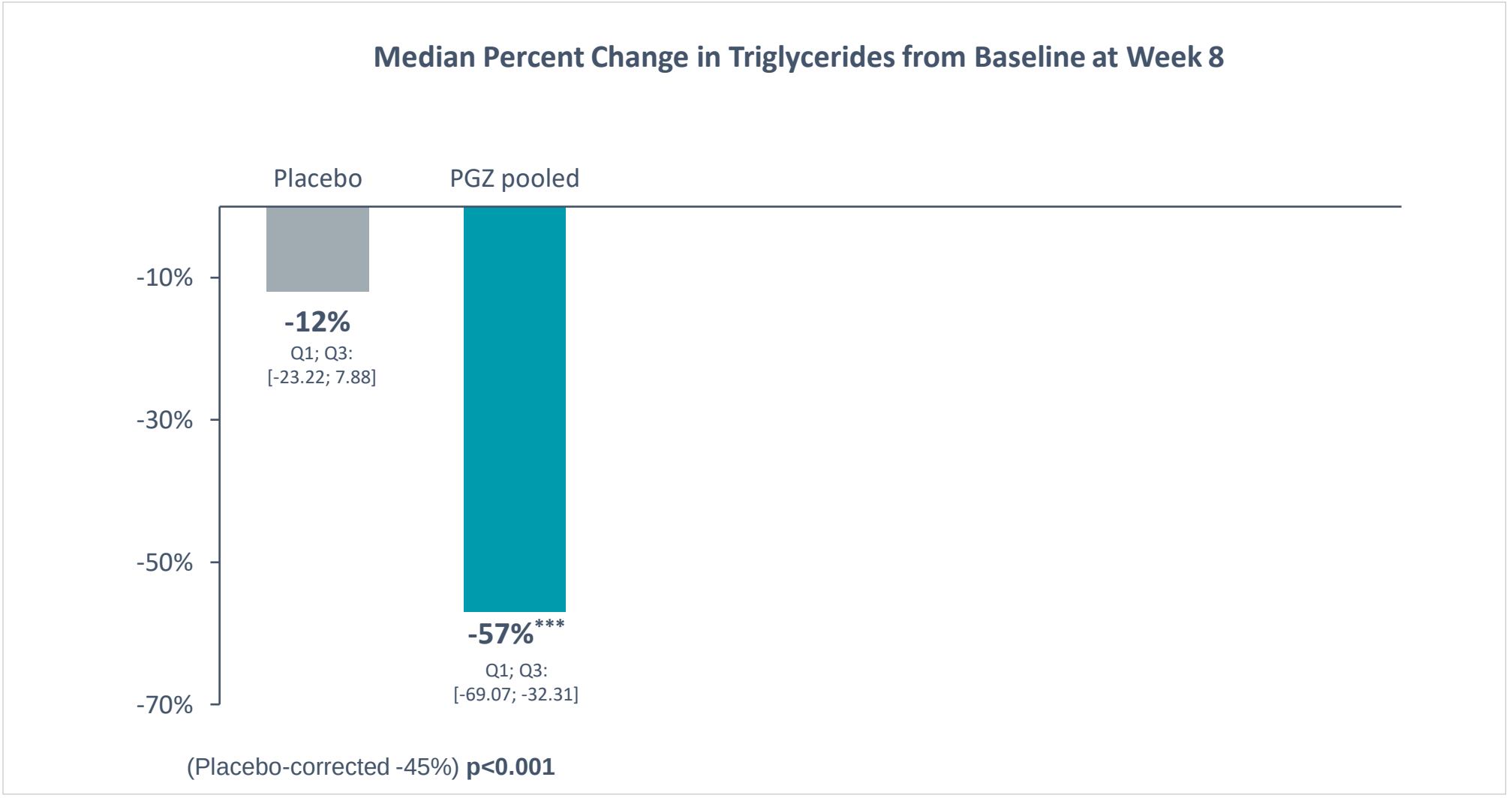
	Placebo (n=18)	PGZ Pooled (n=67)	PGZ 9mg QW (n=12)	PGZ 18mg QW (n=21)	PGZ 27mg QW (n=18)	PGZ 36mg Q2W (n=16)
Serious adverse event (unrelated)	0	1*	0	0	1	0
Treatment emergent discontinuations (related/unrelated)	0	2^/2	0	0	2^/2	0

*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

Pegozafermin Significantly Reduced Triglycerides Across All Dose Groups

Primary endpoint



p value vs placebo for change from baseline based on van Elteren Test with adjustment for stratification factors
Full Analysis Set; *** p<0.001 versus placebo

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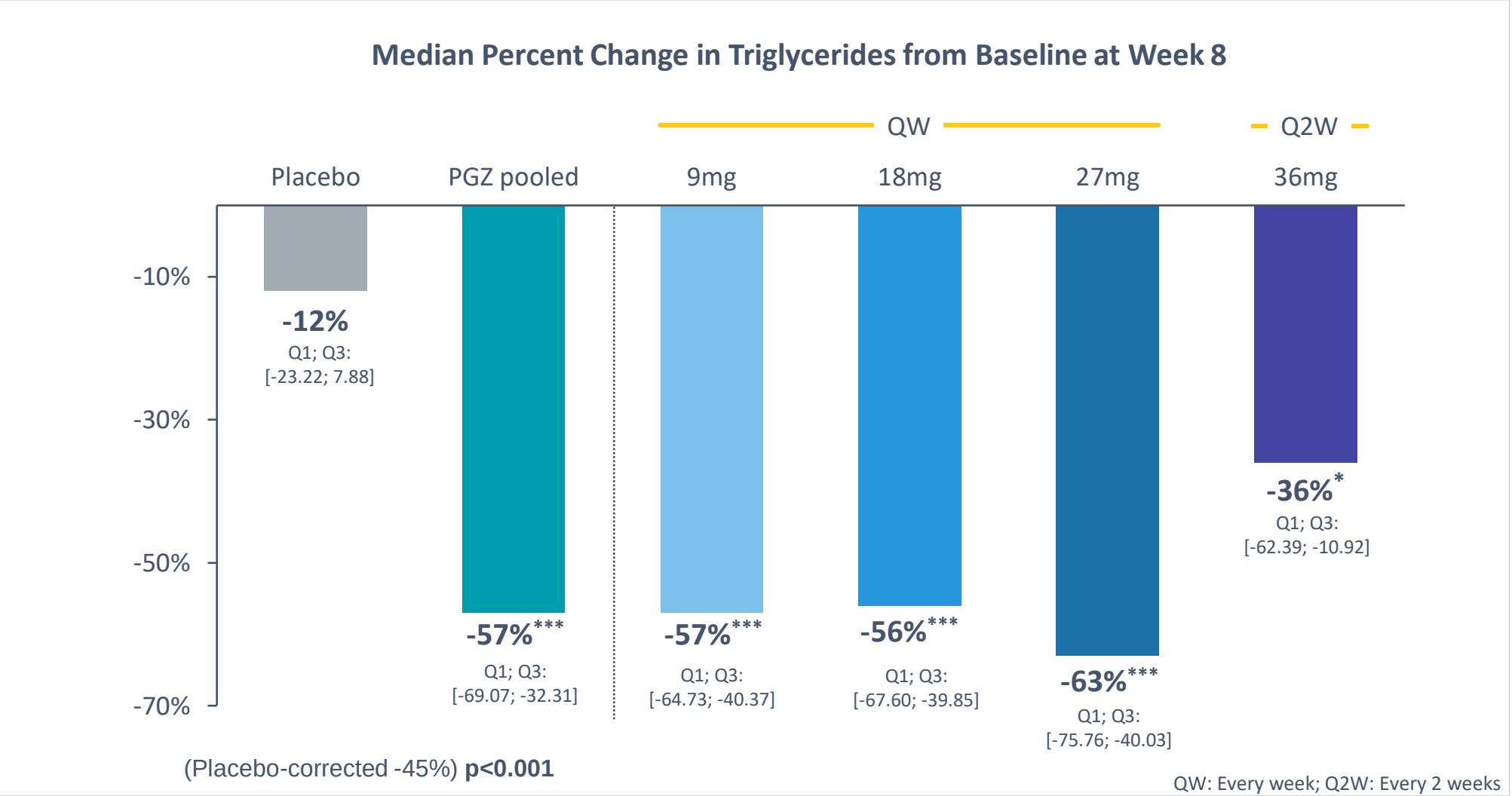
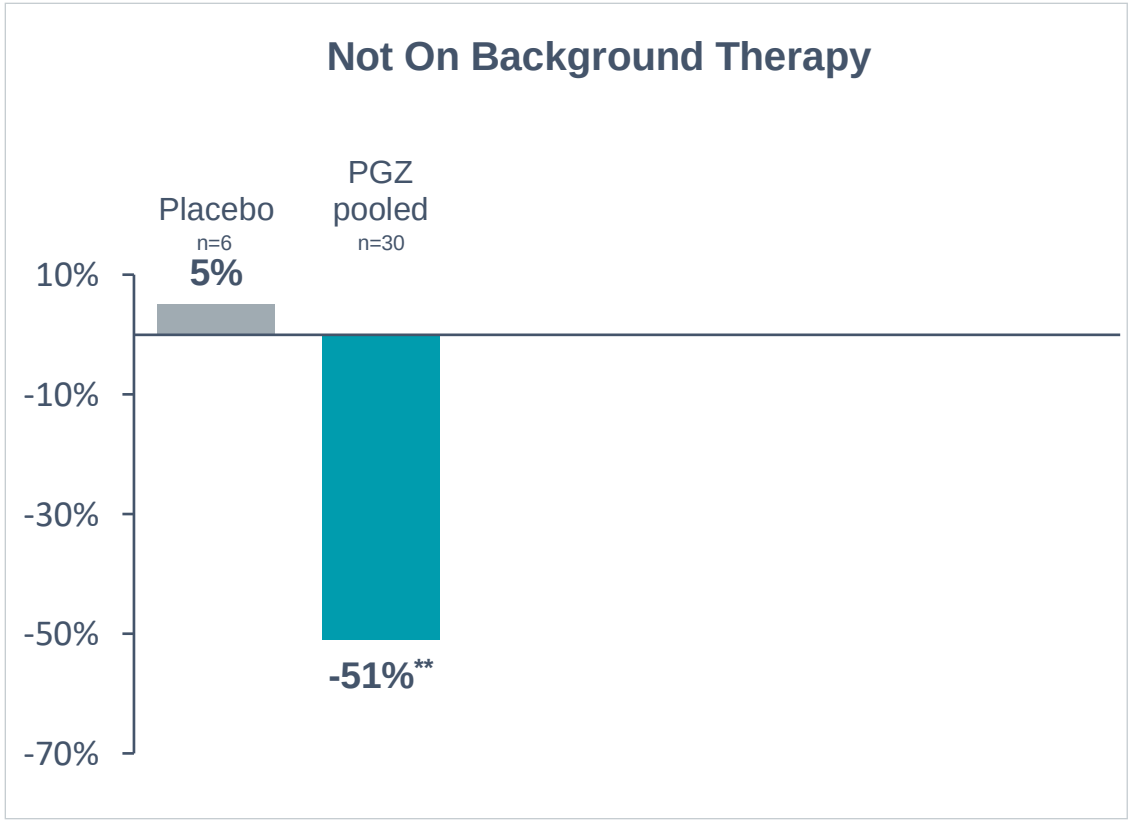
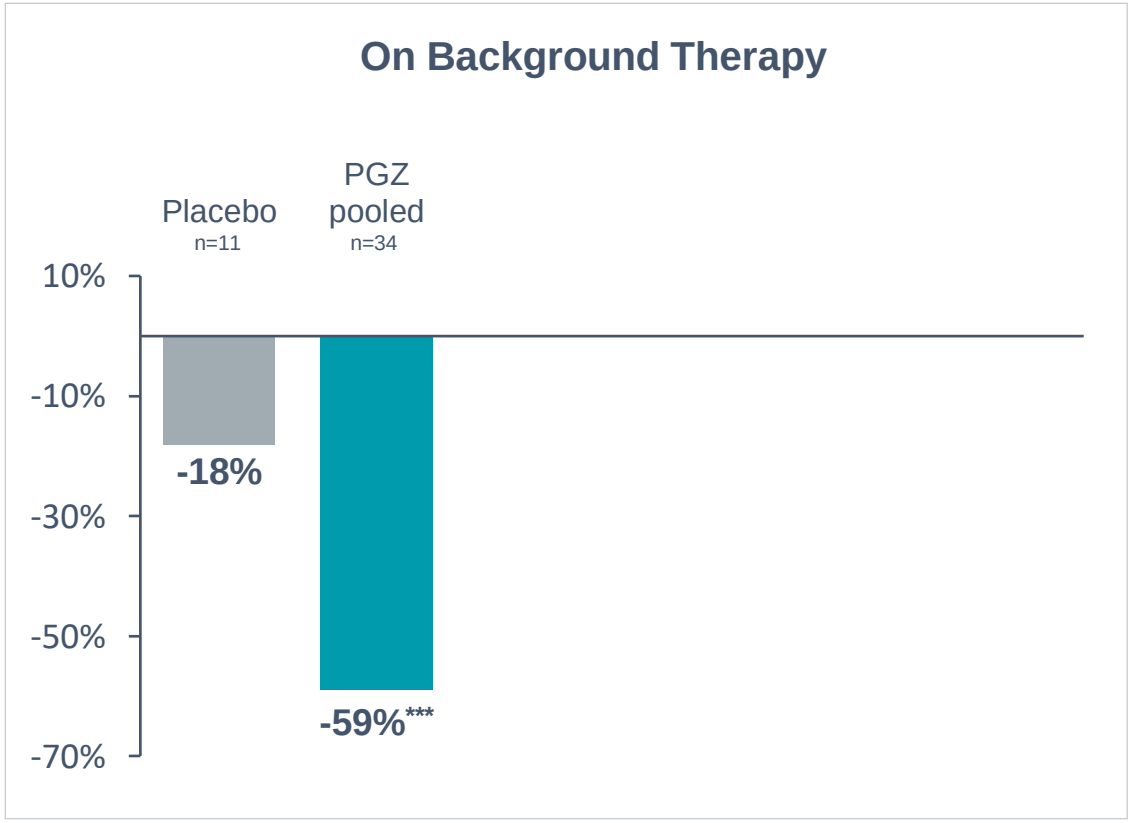


p value vs placebo for change from baseline for individual dose arm is based on Wilcoxon Rank-Sum Test
Full Analysis Set; * p<0.05; *** p<0.001 versus placebo

Pegozafermin Treatment Led to a Significant Reduction in Triglycerides Irrespective of Background Therapy

Median Percent Change in Triglycerides from Baseline at Week 8



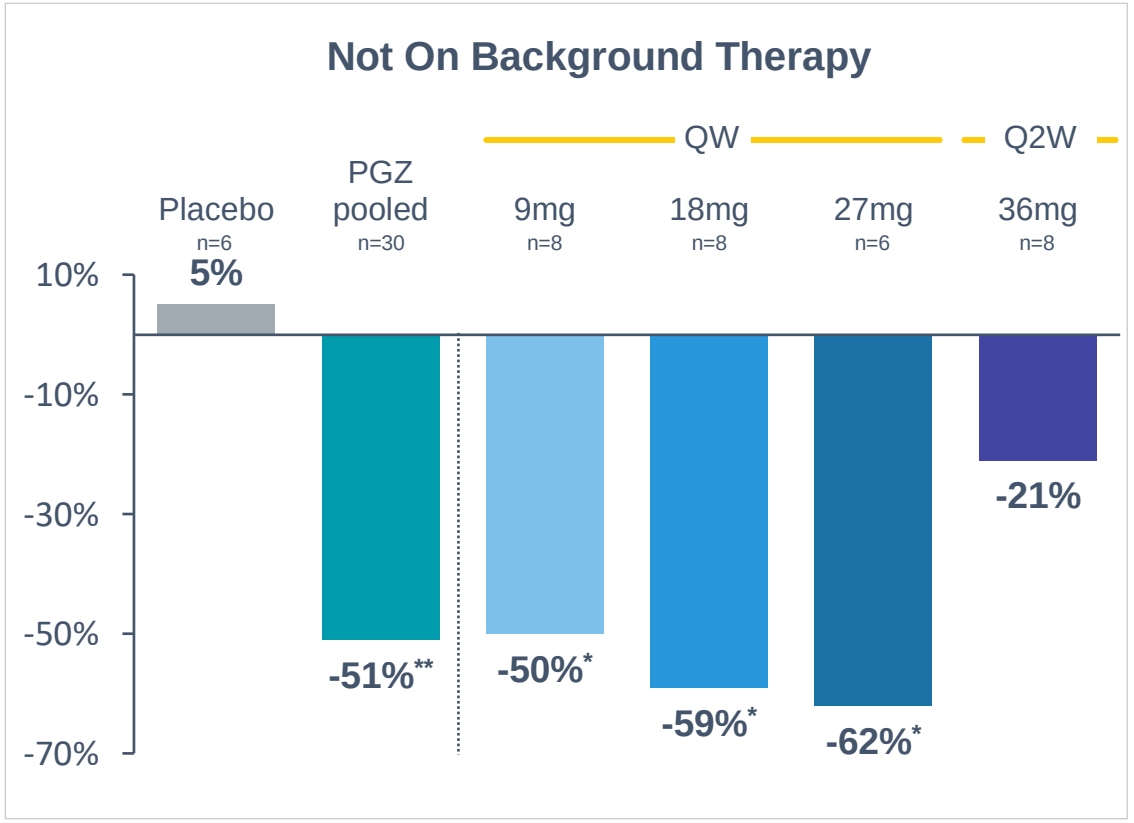


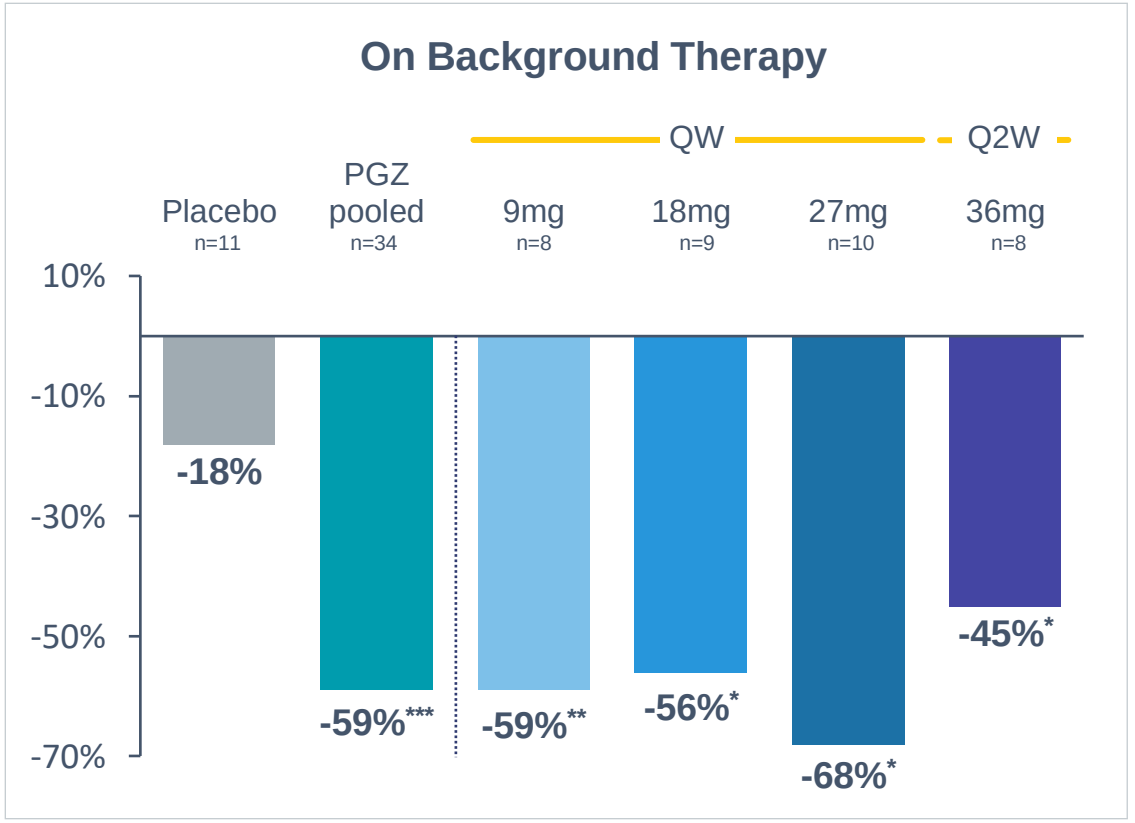
Results are consistent with data from patients on background therapy of statins or statin combos, prescription omega-3s, and fibrates

p value vs placebo for change from baseline based on Wilcoxon Rank-Sum Test
Full Analysis Set; ** p<0.01;*** p<0.001 versus placebo

Pegozafermin Treatment Led to a Significant Reduction in Triglycerides Irrespective of Background Therapy

Median Percent Change in Triglycerides from Baseline at Week 8

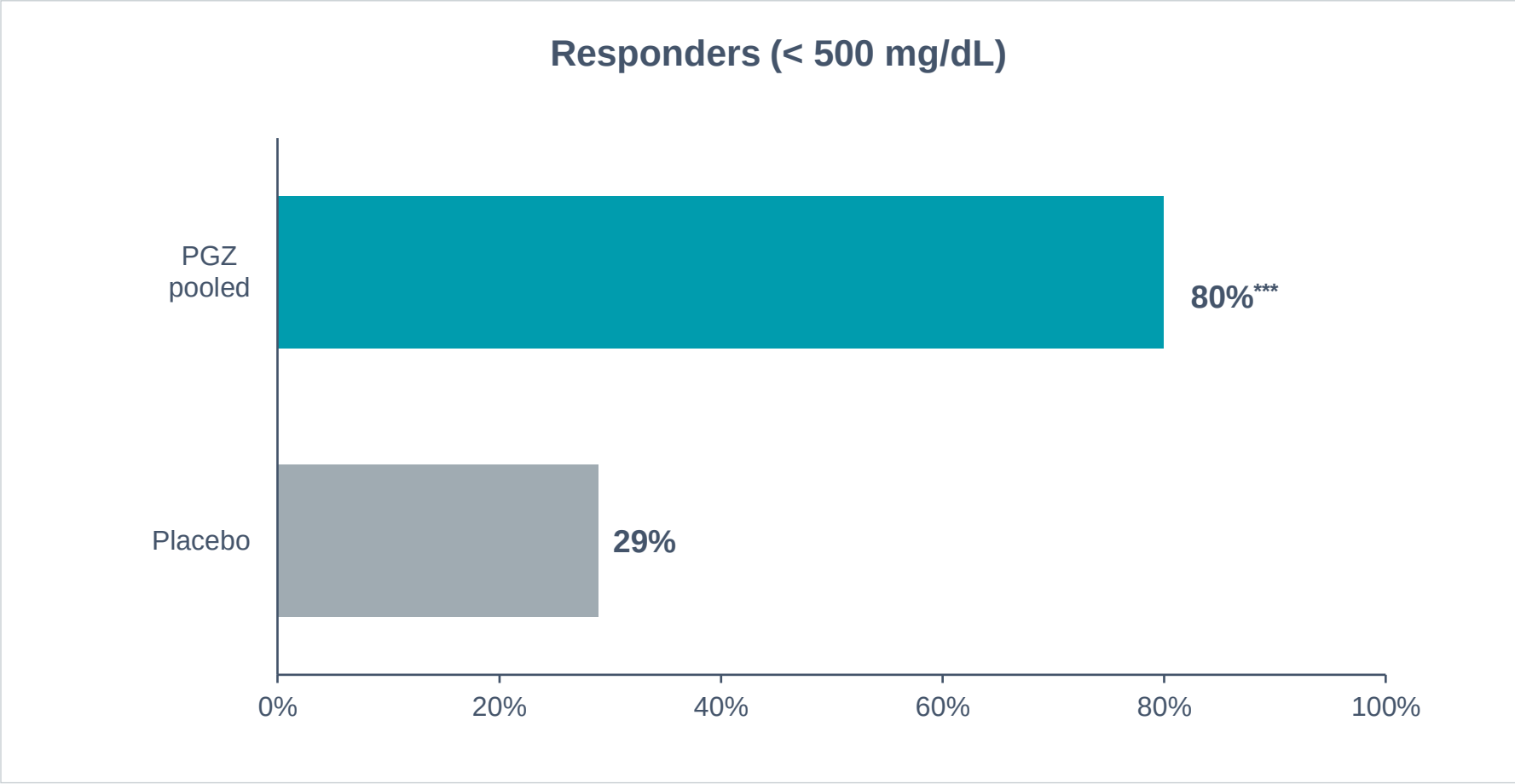




Results are consistent with data from patients on background therapy of statins or statin combos, prescription omega-3s, and fibrates

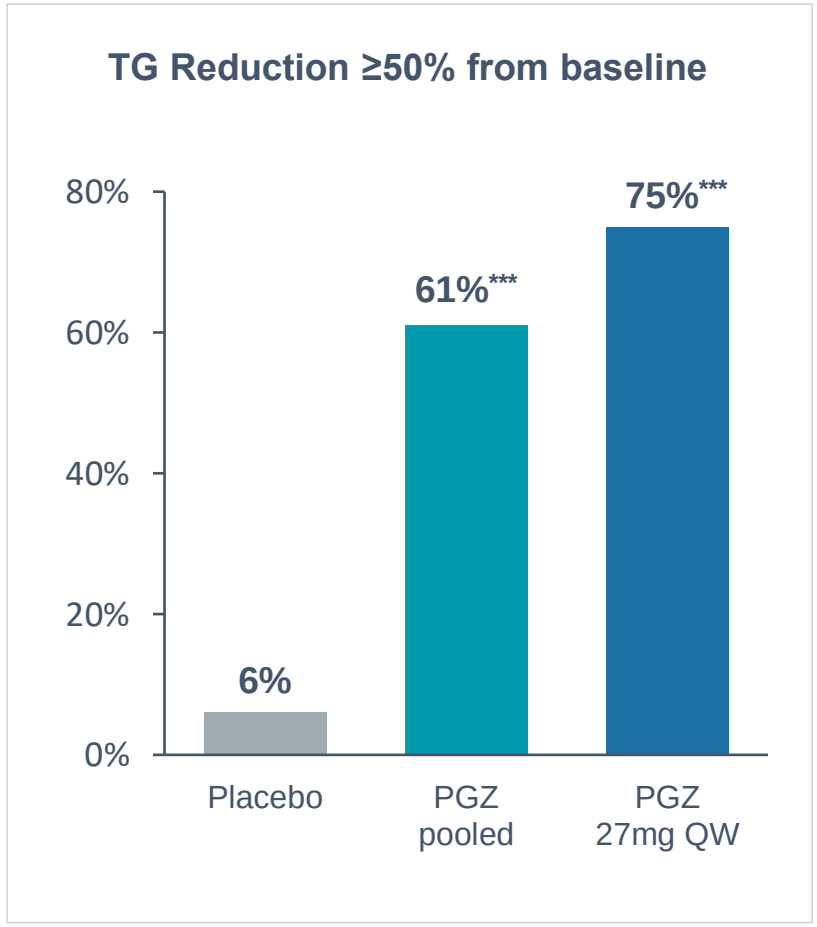
p value vs placebo for change from baseline based on Wilcoxon Rank-Sum Test
Full Analysis Set; * p<0.05; ** p<0.01;*** p<0.001 versus placebo

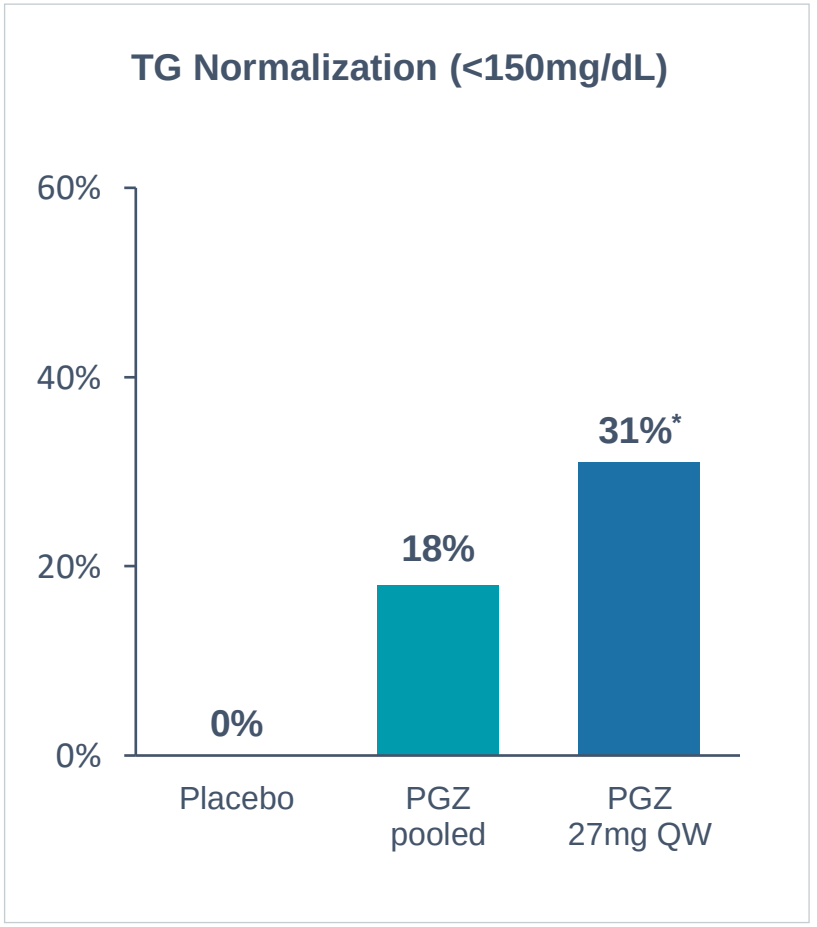
Most Pegozafermin Treated Patients Reach Initial Treatment Goal



Analysis via CMH and Chi-square test comparing the pooled and individual PGZ groups vs placebo respectively
Full Analysis Set; *** p<0.001
TG Responders defined as patients who achieve TG <500 mg/dL

Substantial Proportion of Patients Achieved Key Metrics with Pegozafermin 27 mg QW



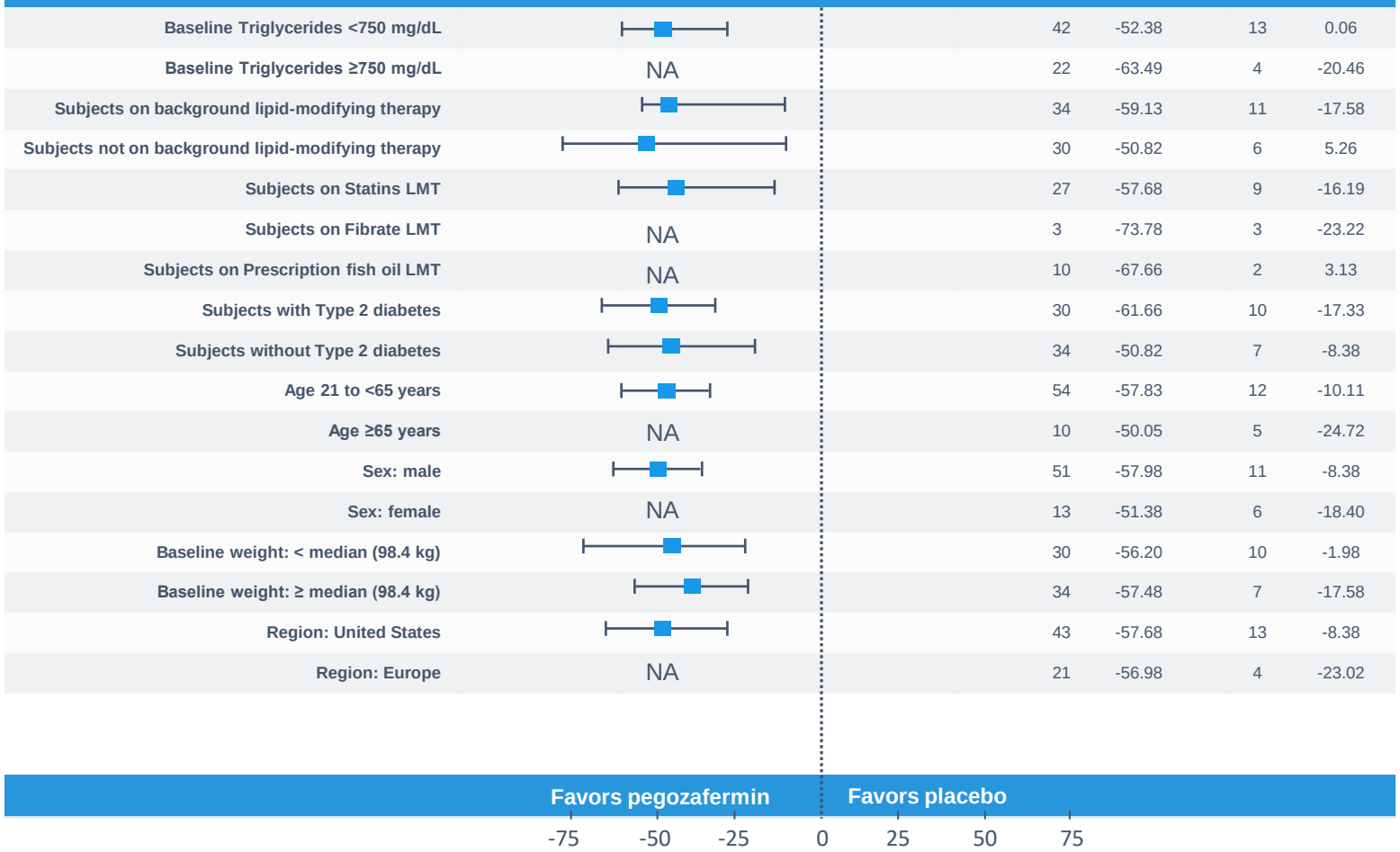


Analysis via CMH and Chi-square test comparing the pooled and individual PGZ groups vs placebo respectively
Full Analysis Set; * p<0.05; *** p<0.001
TG Responders defined as patients who achieve TG <500 mg/dL

Pegozafermin Showed Consistent and Significant Benefit in Triglyceride Reduction across All Prespecified Subgroups

Median Percent Change in Triglycerides from Baseline at Week 8

	n	PGZ pooled, median	n	Placebo, median
Baseline Triglycerides <750 mg/dL	42	-52.38	13	0.06
Baseline Triglycerides ≥750 mg/dL	22	-63.49	4	-20.46
Subjects on background lipid-modifying therapy	34	-59.13	11	-17.58
Subjects not on background lipid-modifying therapy	30	-50.82	6	5.26
Subjects on Statins LMT	27	-57.68	9	-16.19
Subjects on Fibrate LMT	3	-73.78	3	-23.22
Subjects on Prescription fish oil LMT	10	-67.66	2	3.13
Subjects with Type 2 diabetes	30	-61.66	10	-17.33
Subjects without Type 2 diabetes	34	-50.82	7	-8.38
Age 21 to <65 years	54	-57.83	12	-10.11
Age ≥65 years	10	-50.05	5	-24.72
Sex: male	51	-57.98	11	-8.38
Sex: female	13	-51.38	6	-18.40
Baseline weight: < median (98.4 kg)	30	-56.20	10	-1.98
Baseline weight: ≥ median (98.4 kg)	34	-57.48	7	-17.58
Region: United States	43	-57.68	13	-8.38
Region: Europe	21	-56.98	4	-23.02

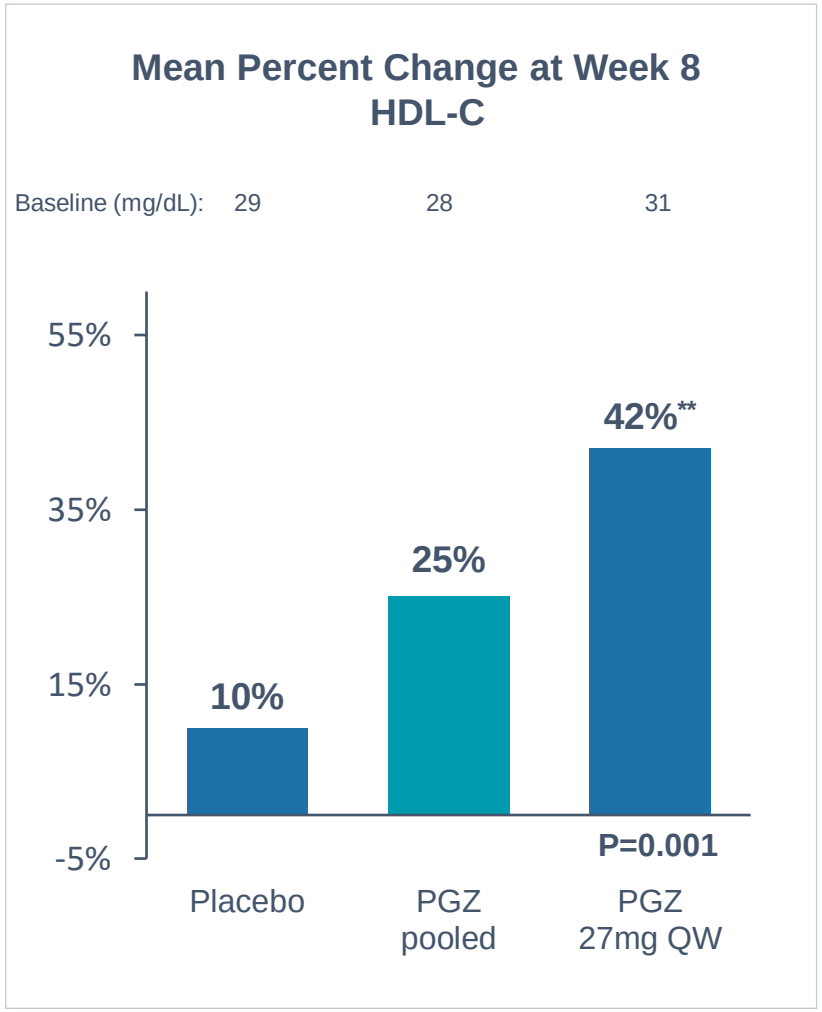


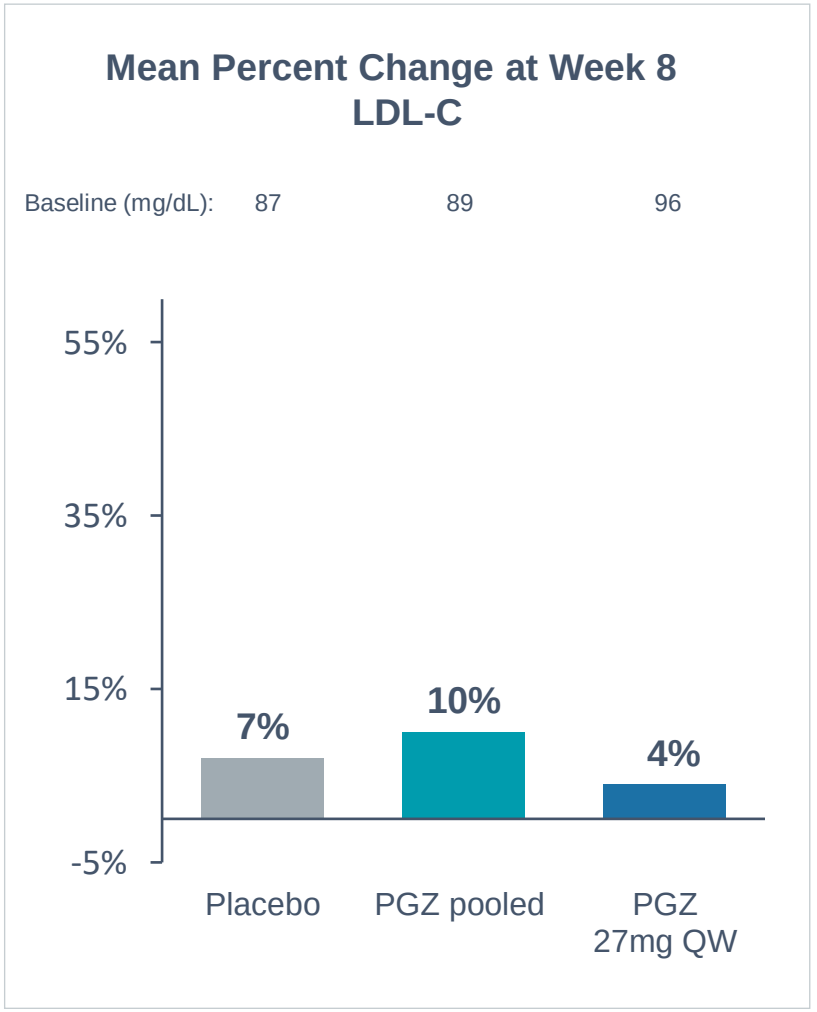
NA – Not analyzed*

95% confidence interval for median difference

*If the percentage of subjects within a certain subgroup was less than 33% of the overall cohort, only descriptive analysis is presented

Pegozafermin Increased HDL-C with Minimal Impact on LDL-C

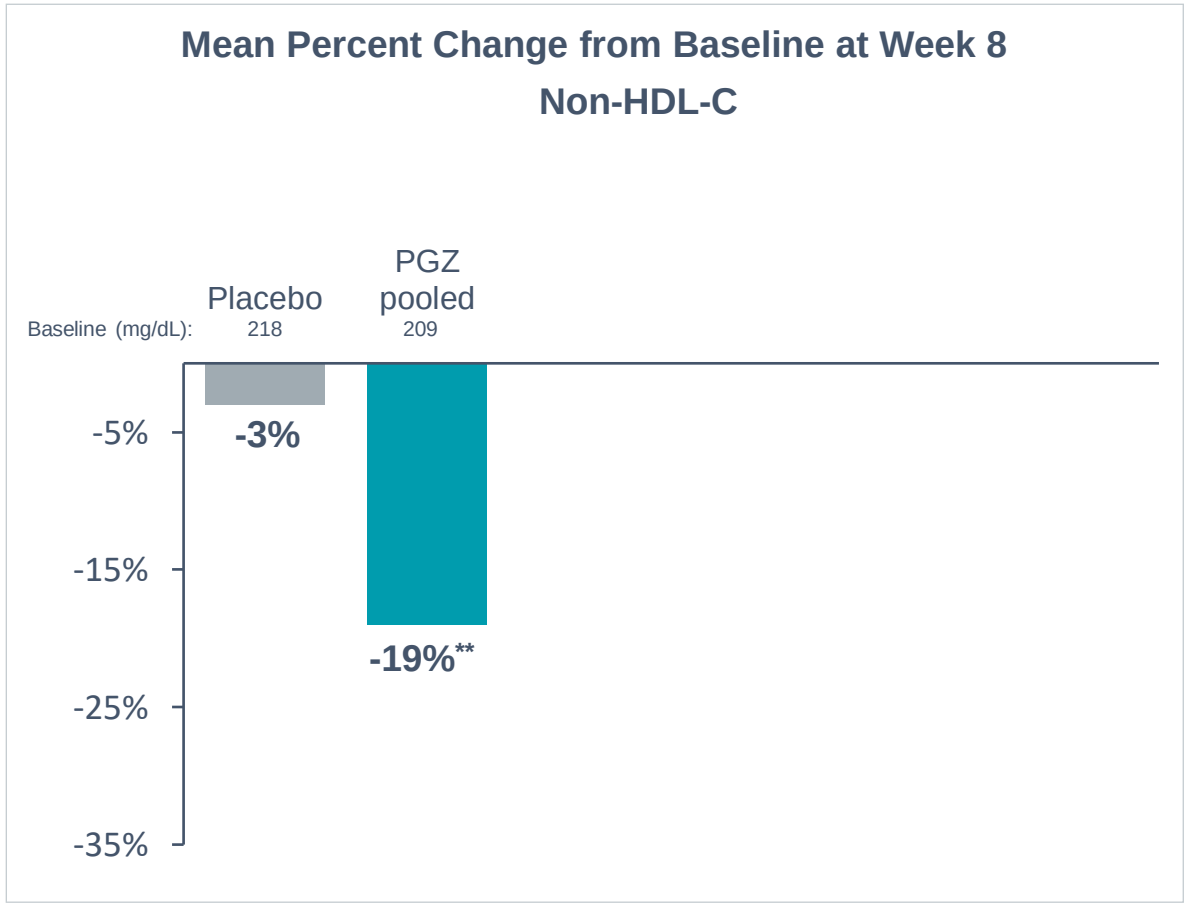


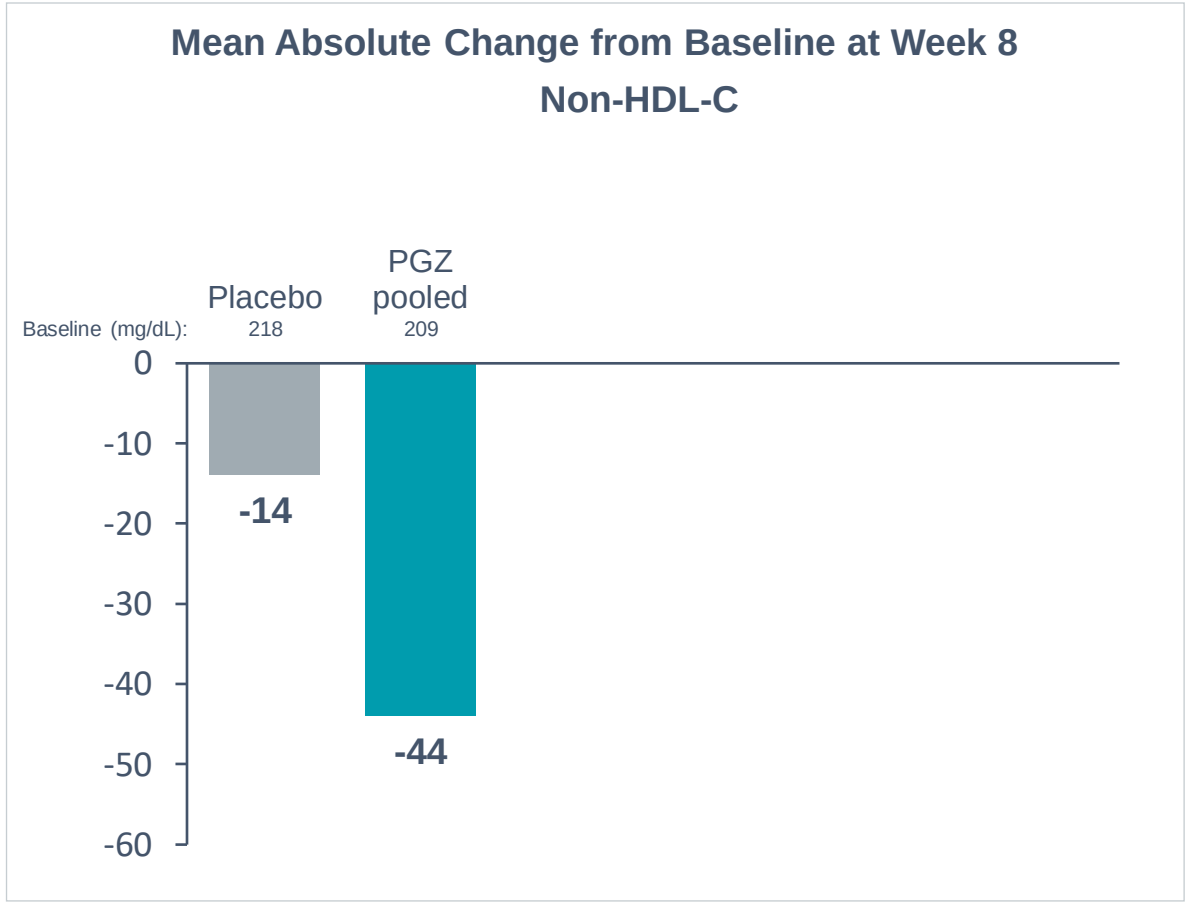


Full Analysis Set; ** p=0.01 versus placebo based on MMRM analysis

Pegozafermin Demonstrated Reduction in Non-HDL-C

Absolute Non-HDL-C reduction is associated with MACE improvement

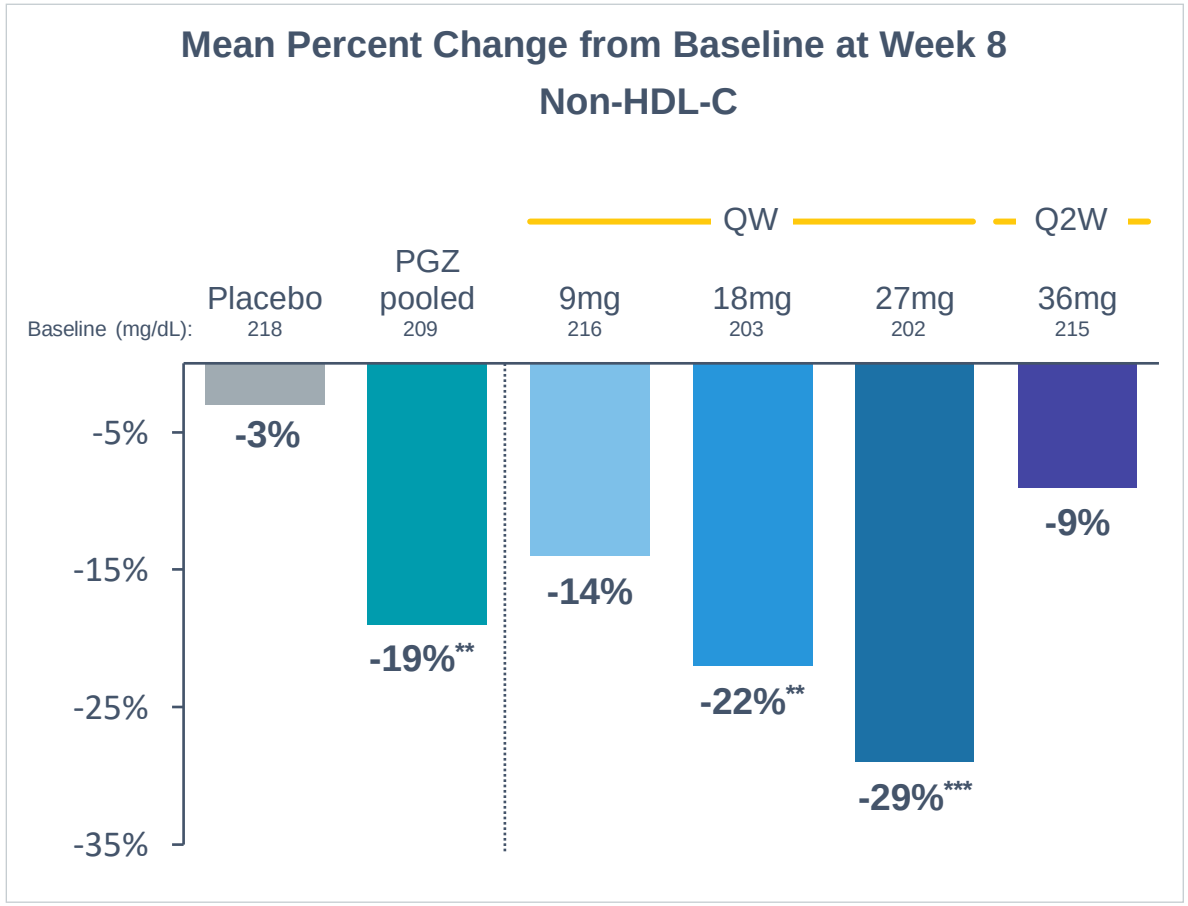


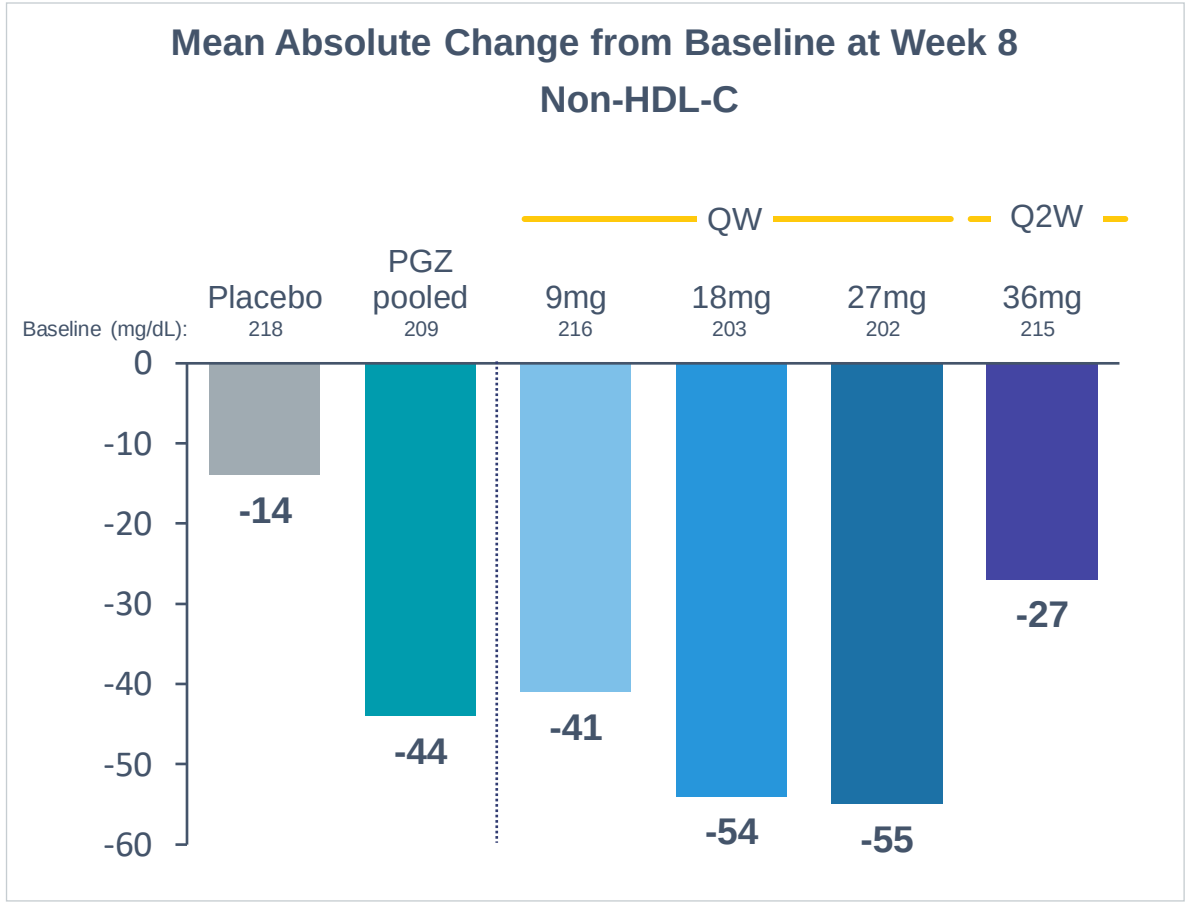


Full Analysis Set; ** p<0.01 versus placebo based on MMRM analysis; only descriptive analysis was performed for mean absolute change comparison

Pegozafermin Demonstrated Reduction in Non-HDL-C

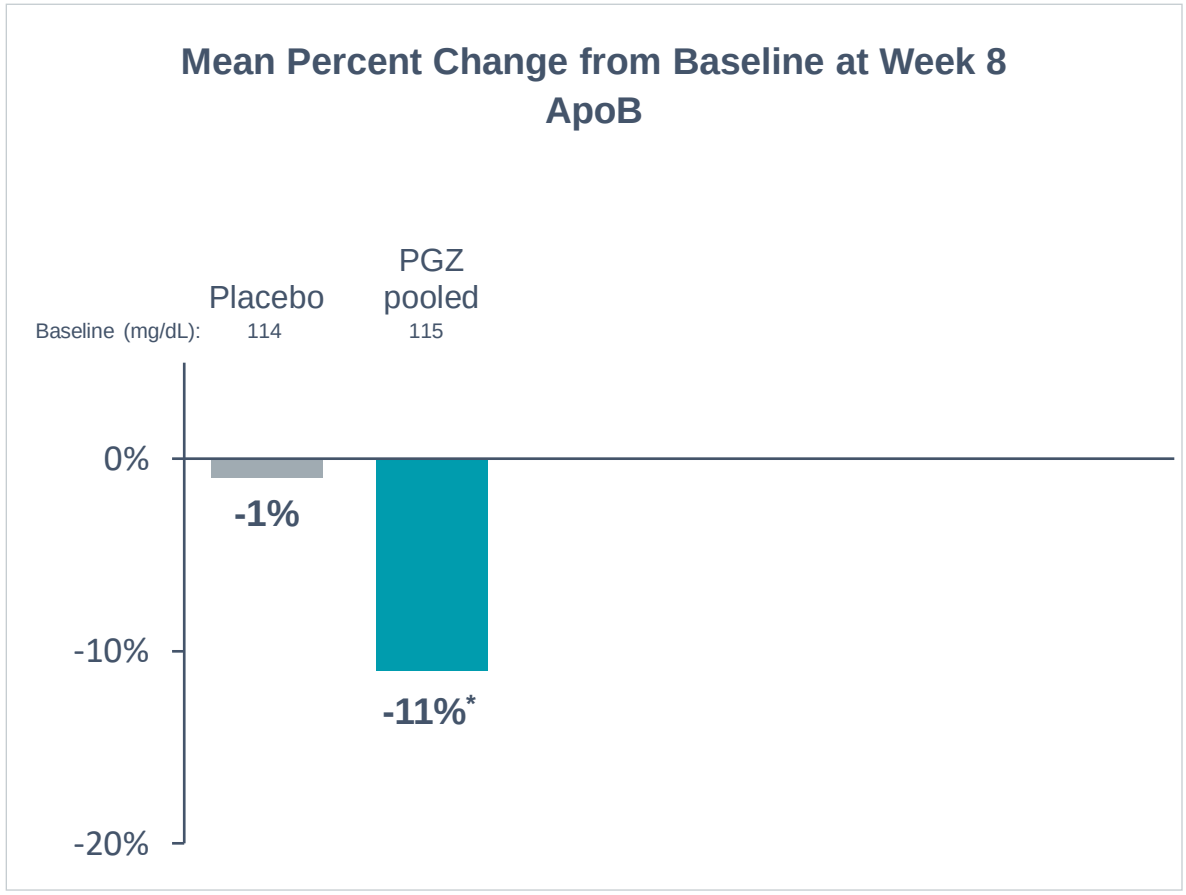
Absolute non-HDL-C reduction is associated with MACE improvement

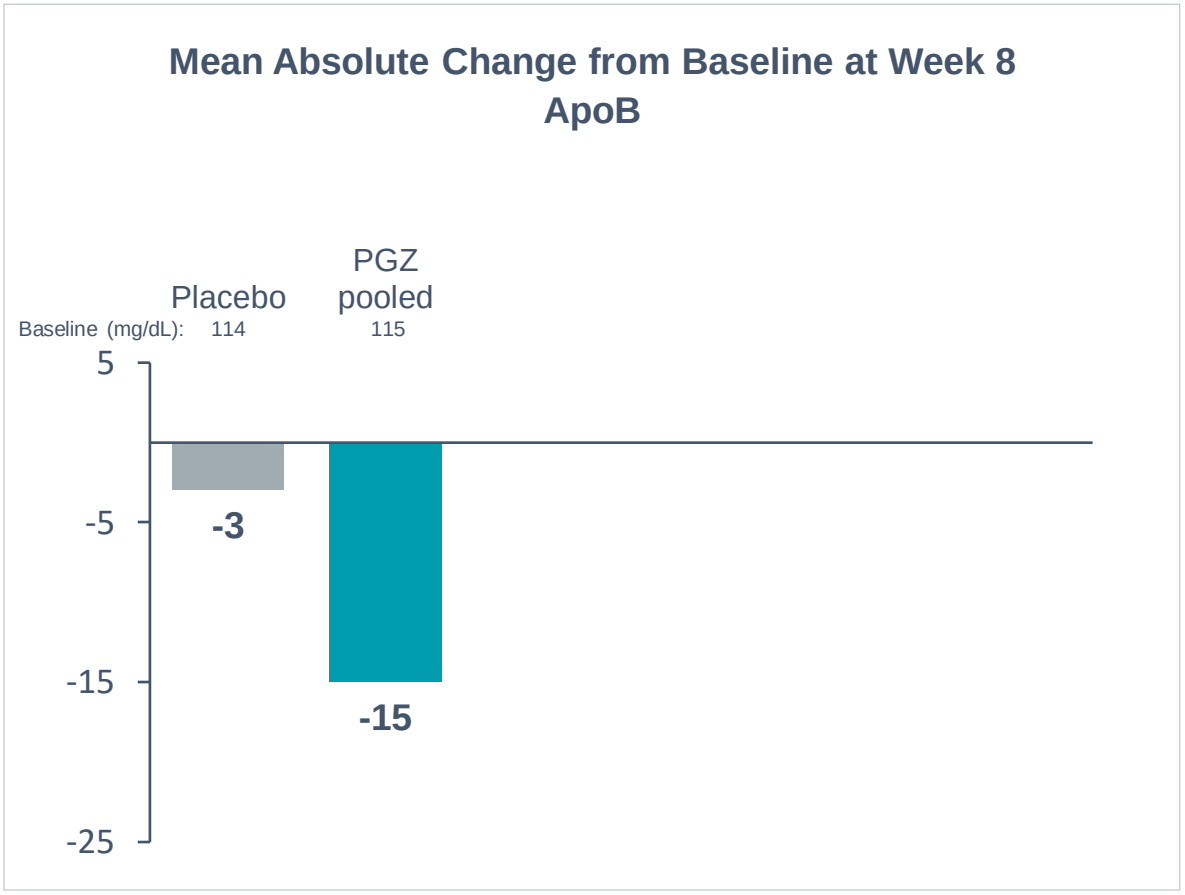




Full Analysis Set; ** p<0.01, ***p<0.001 versus placebo based on MMRM analysis; only descriptive analysis was performed for mean absolute change comparison

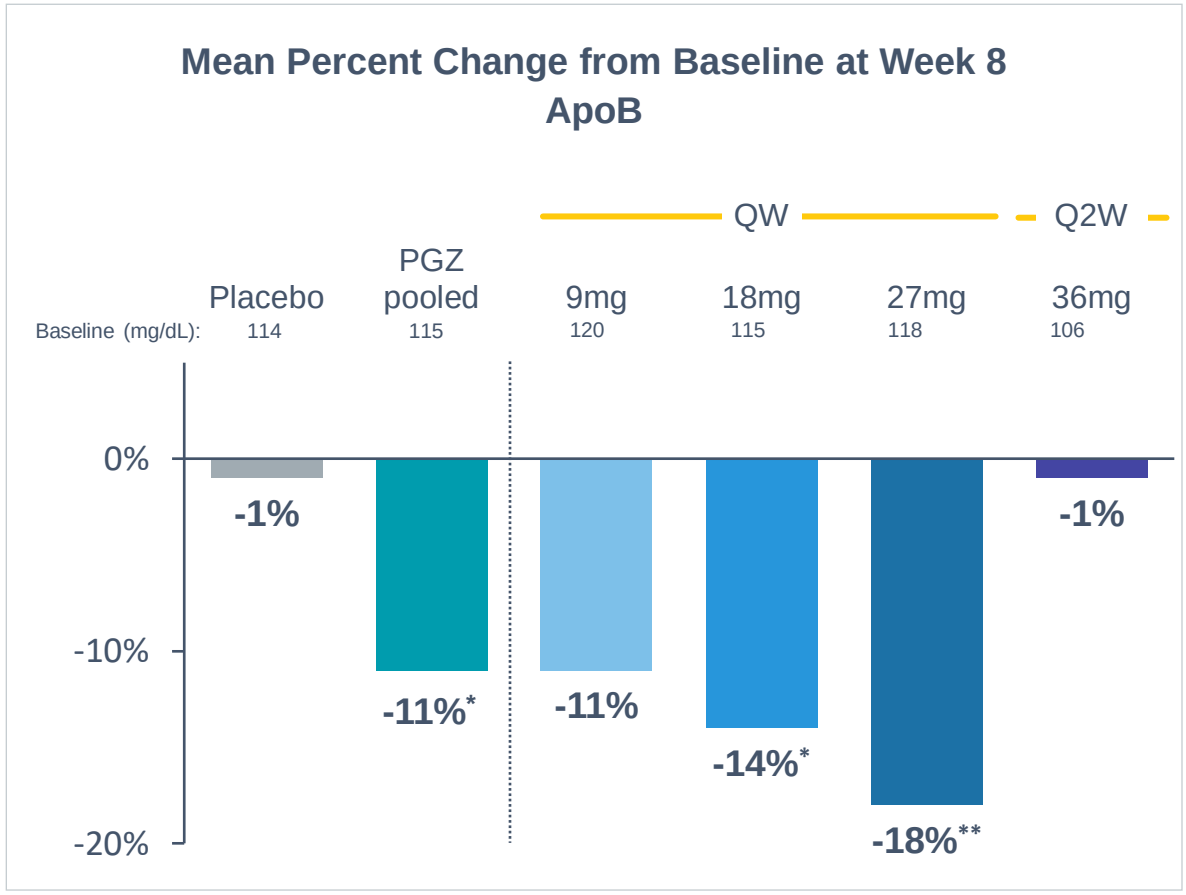
Pegozafermin Demonstrated Clinically Meaningful Improvements in ApoB—A Key Marker of Cardiovascular Risk

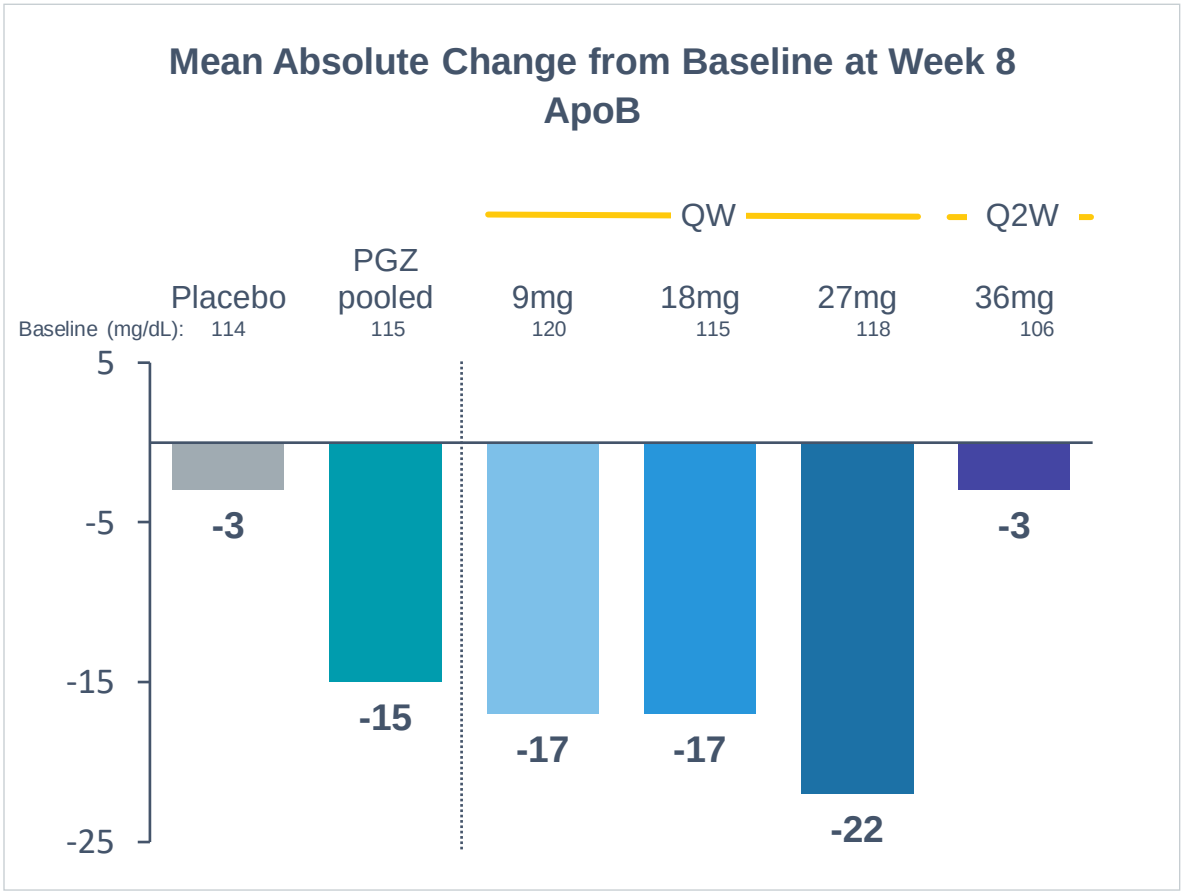




Full Analysis Set; * p<0.05 versus placebo based on MMRM analysis ; only descriptive analysis was performed for mean absolute change comparison

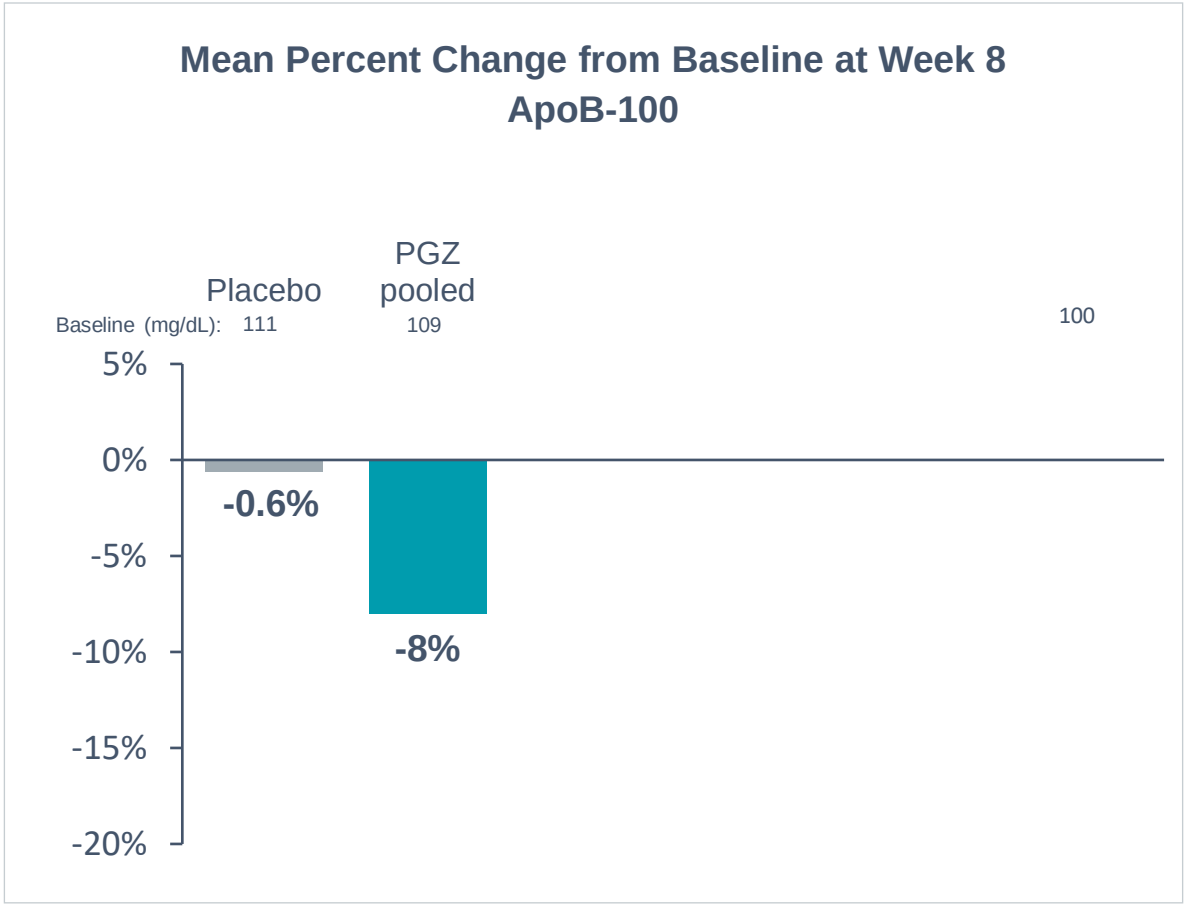
Pegozafermin Demonstrated Clinically Meaningful Improvements in ApoB—A Key Marker of Cardiovascular Risk

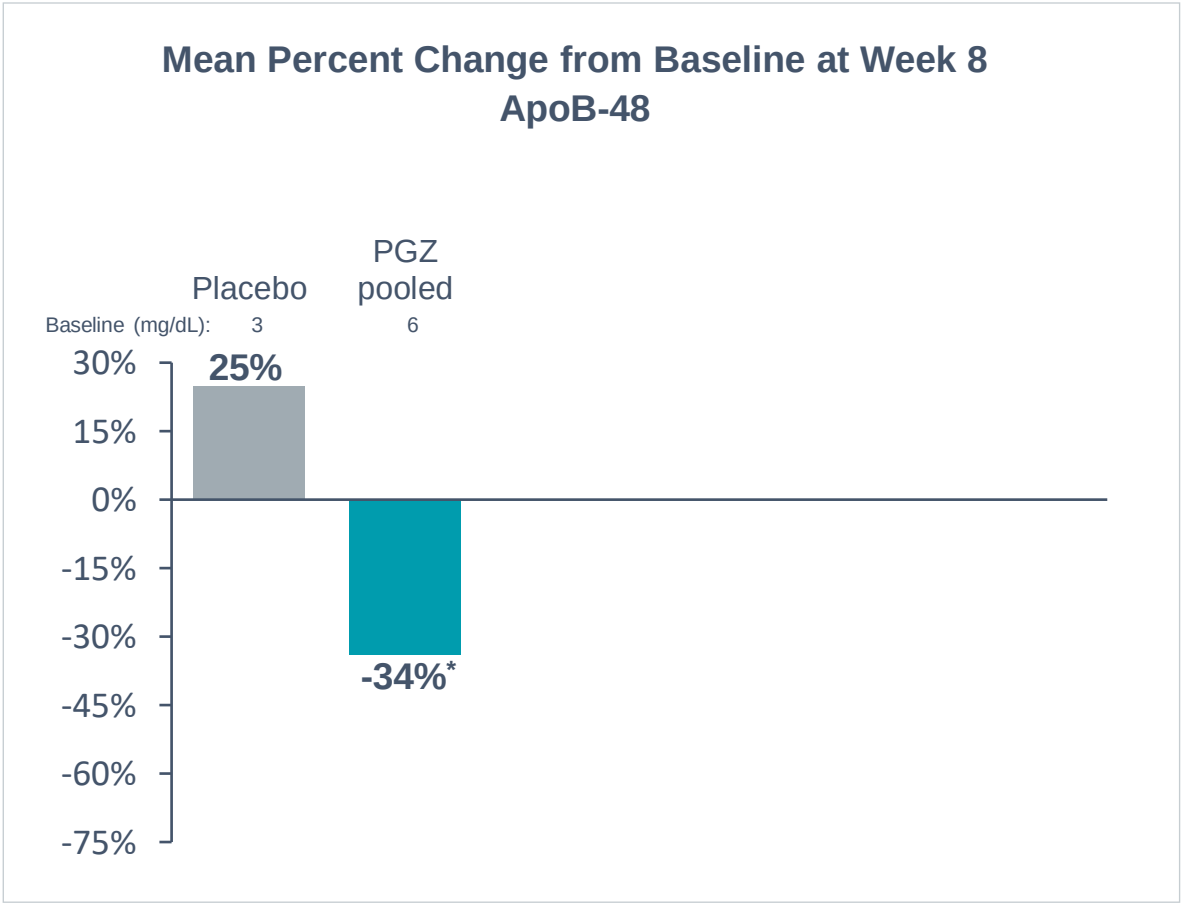




Full Analysis Set; * p<0.05; ** p<0.01 versus placebo based on MMRM analysis ; only descriptive analysis was performed for mean absolute change comparison

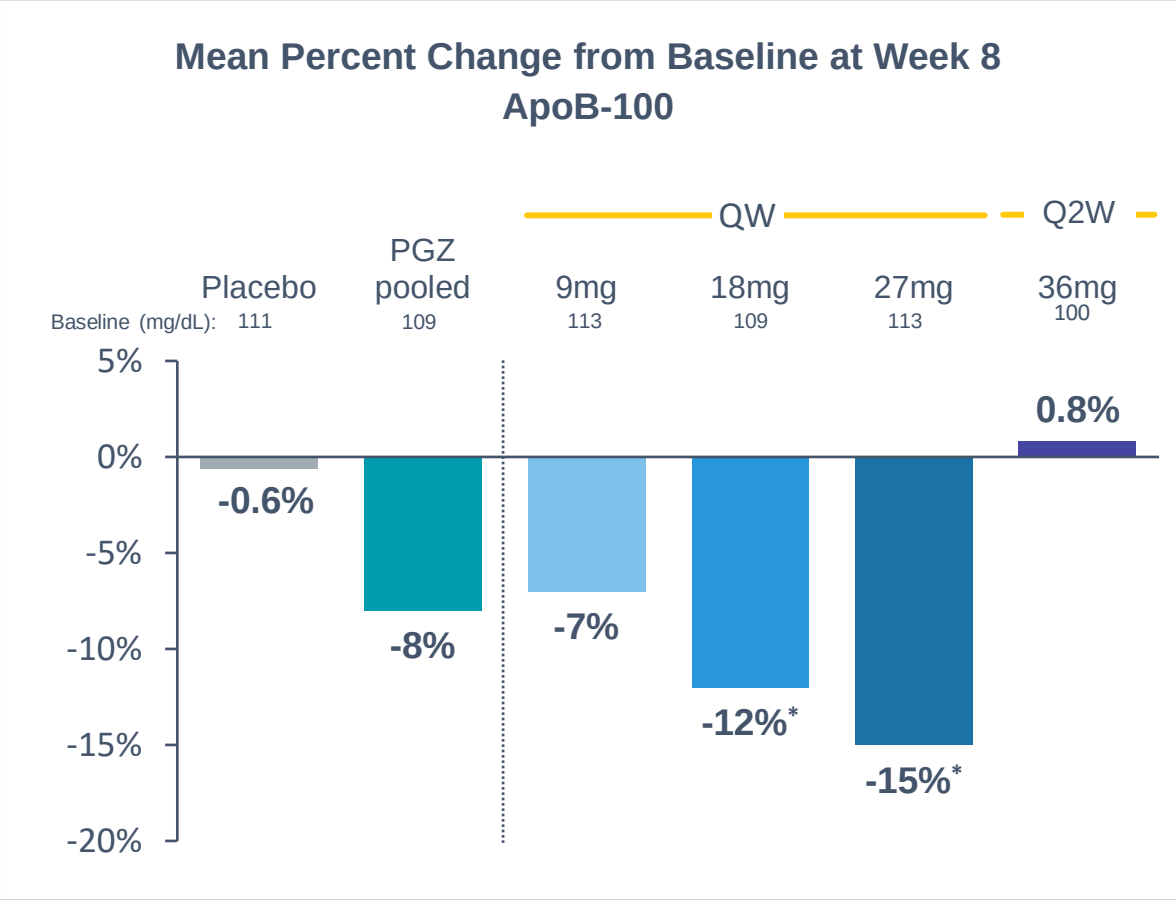
Pegozafermin Demonstrated Reductions Across Subtypes: ApoB-100 and ApoB-48

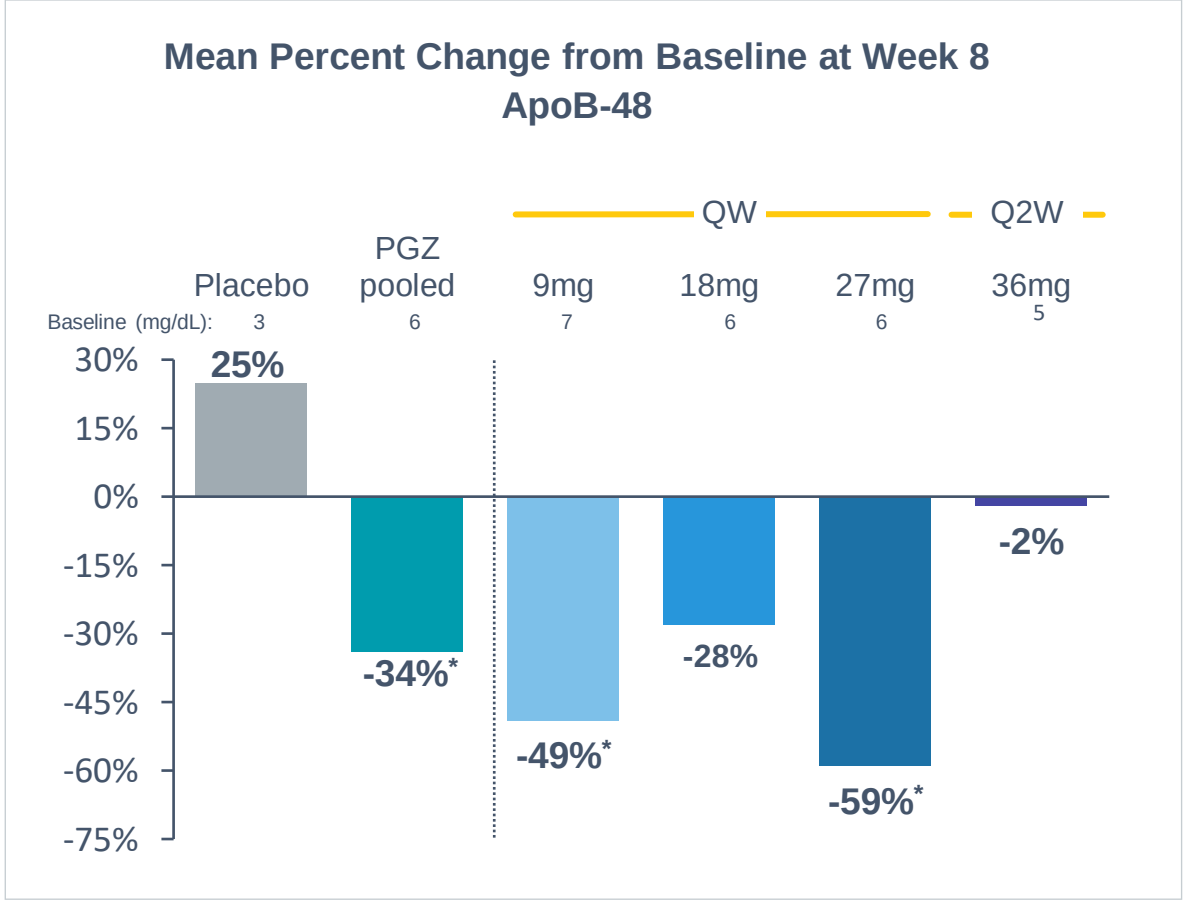




Full Analysis Set; *p<0.05 versus placebo based on MMRM analysis

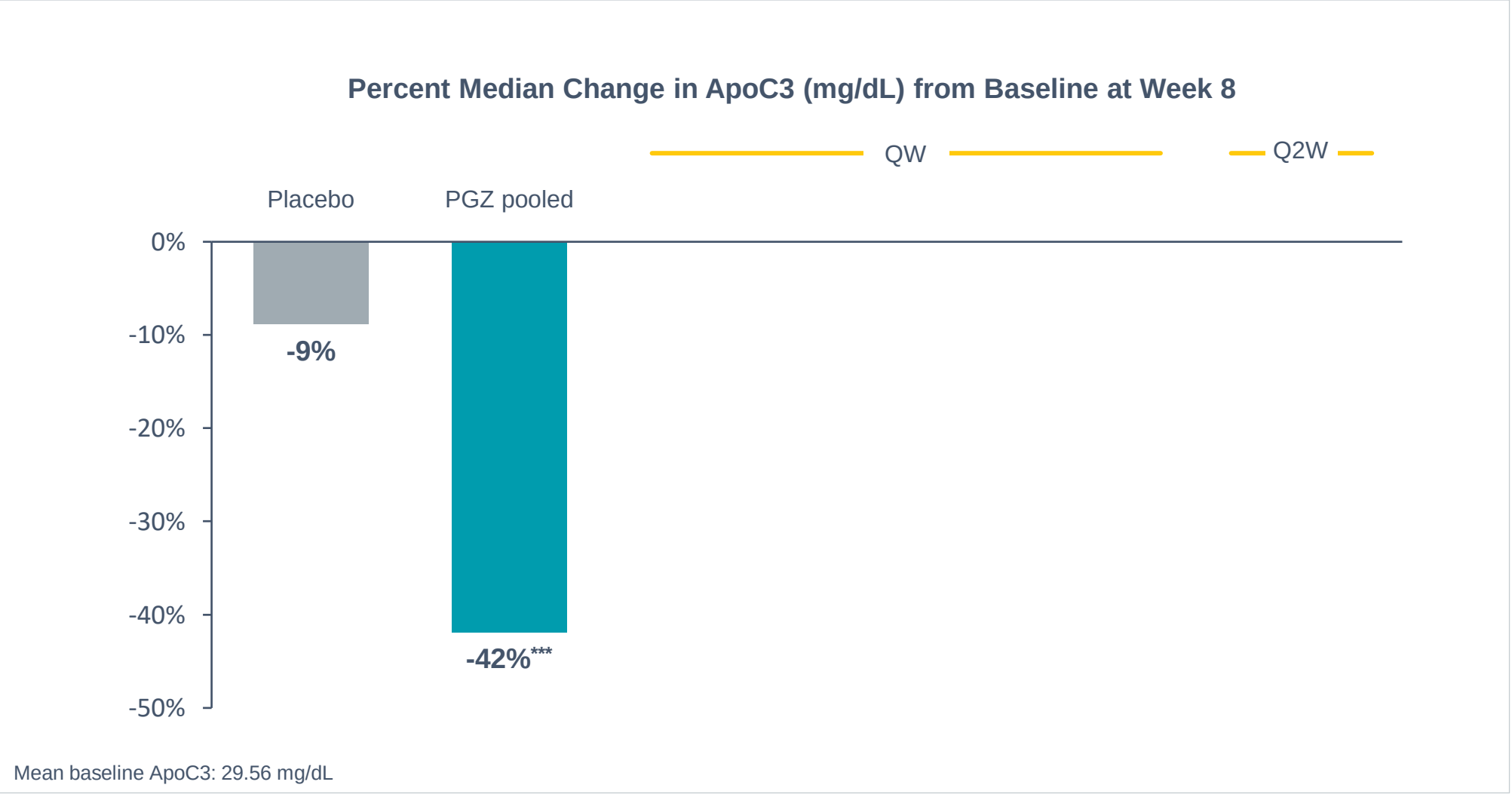
Pegozafermin Demonstrated Reductions Across Subtypes: ApoB-100 and ApoB-48





Full Analysis Set; *p<0.05 versus placebo based on MMRM analysis

Apolipoprotein C3 Levels were Significantly Reduced with Pegozafermin



Full Analysis Set; *** p<0.001 p value vs placebo for change from baseline based on van Elteren Test with adjustment for stratification factors

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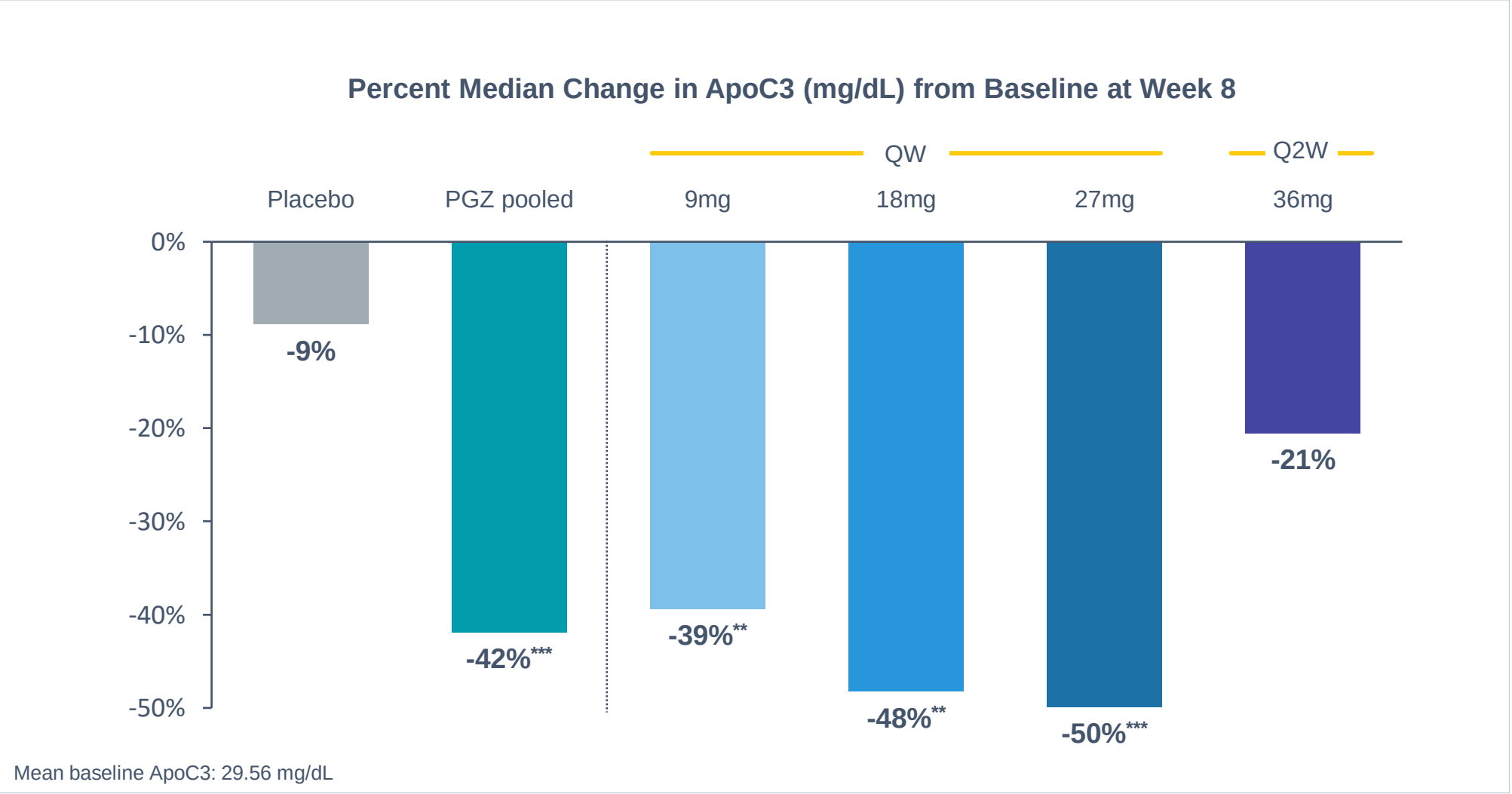
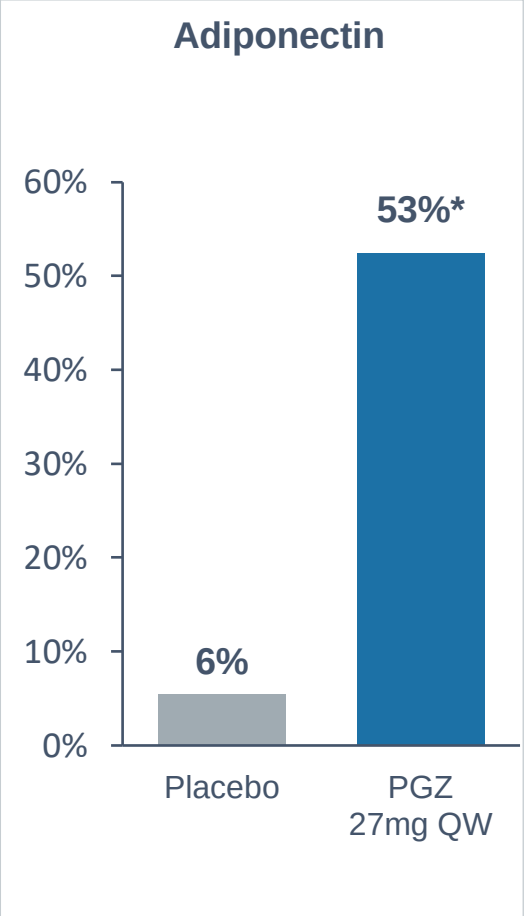


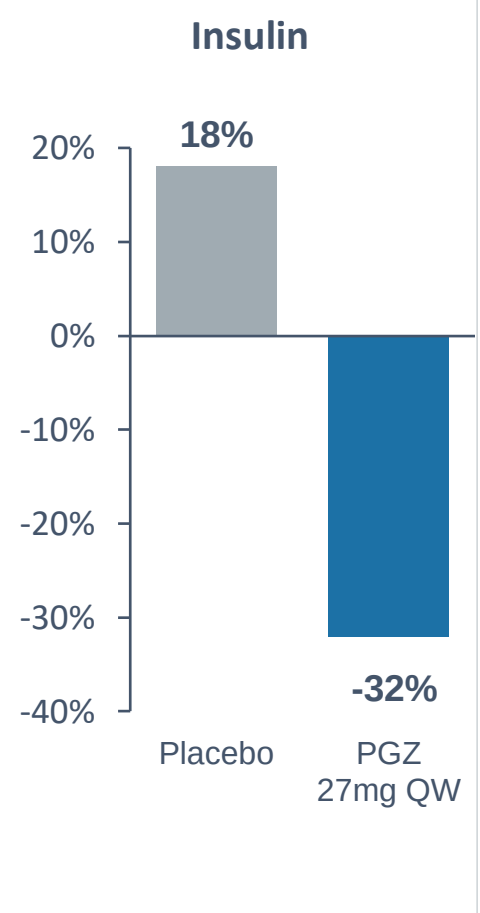
Full Analysis Set; ** p<0.01; *** p<0.001; p value vs placebo for change from baseline for individual dose arm based on Wilcoxon Rank-Sum Test

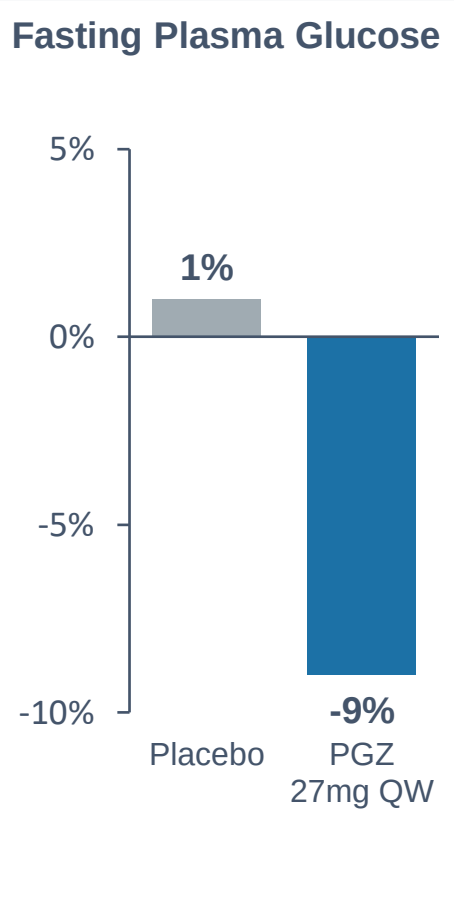
Pegozafermin 27 mg QW Appeared to Improve Insulin Sensitivity

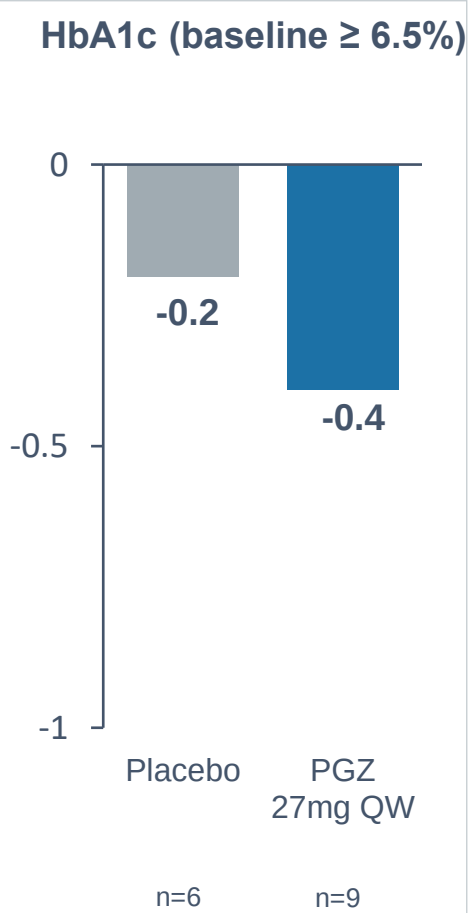
Percent Change

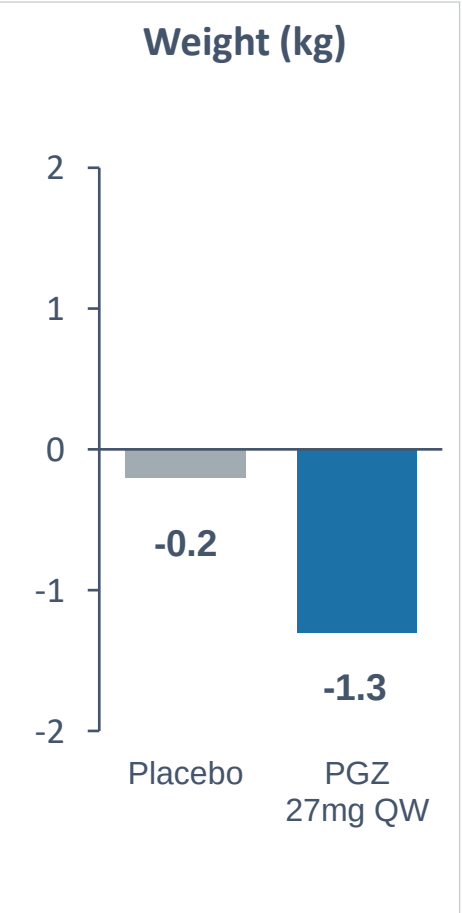
Absolute Change







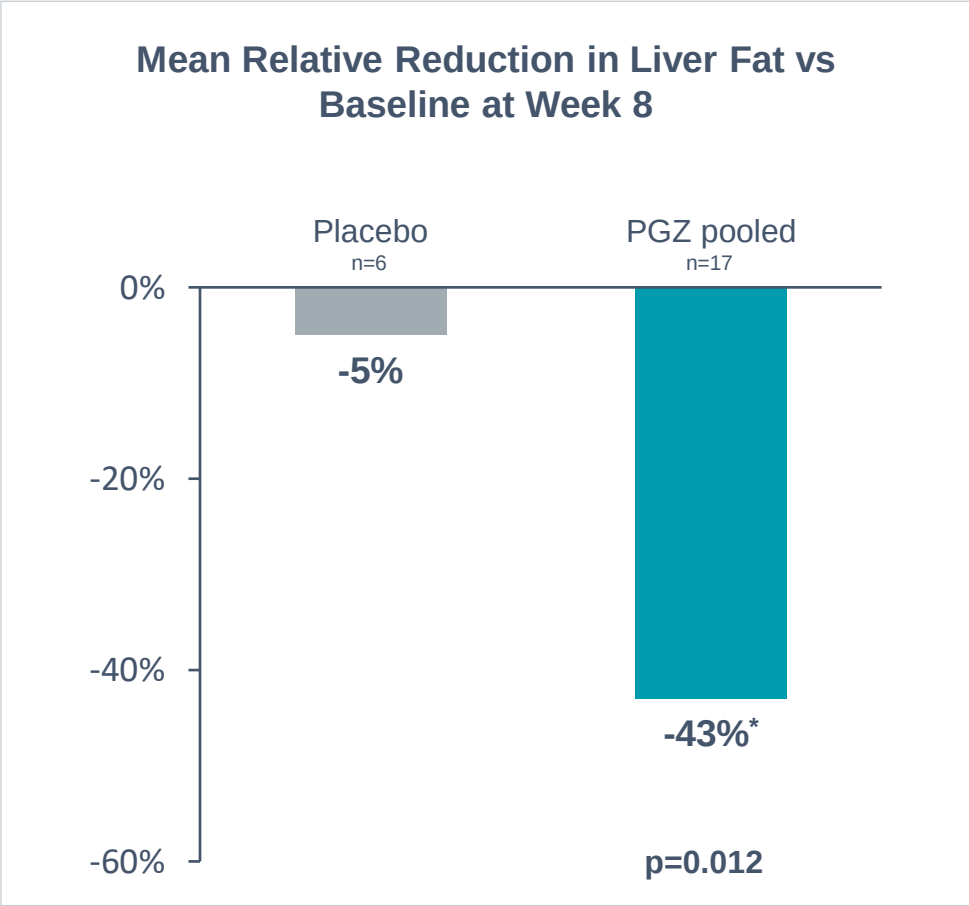




Full Analysis Set; Descriptive analysis
Mean Changes at Week 8; *p=0.017

Pegozafermin Demonstrated Significant Reduction in Liver Fat

Liver fat is an important potentiator of cardiovascular risk

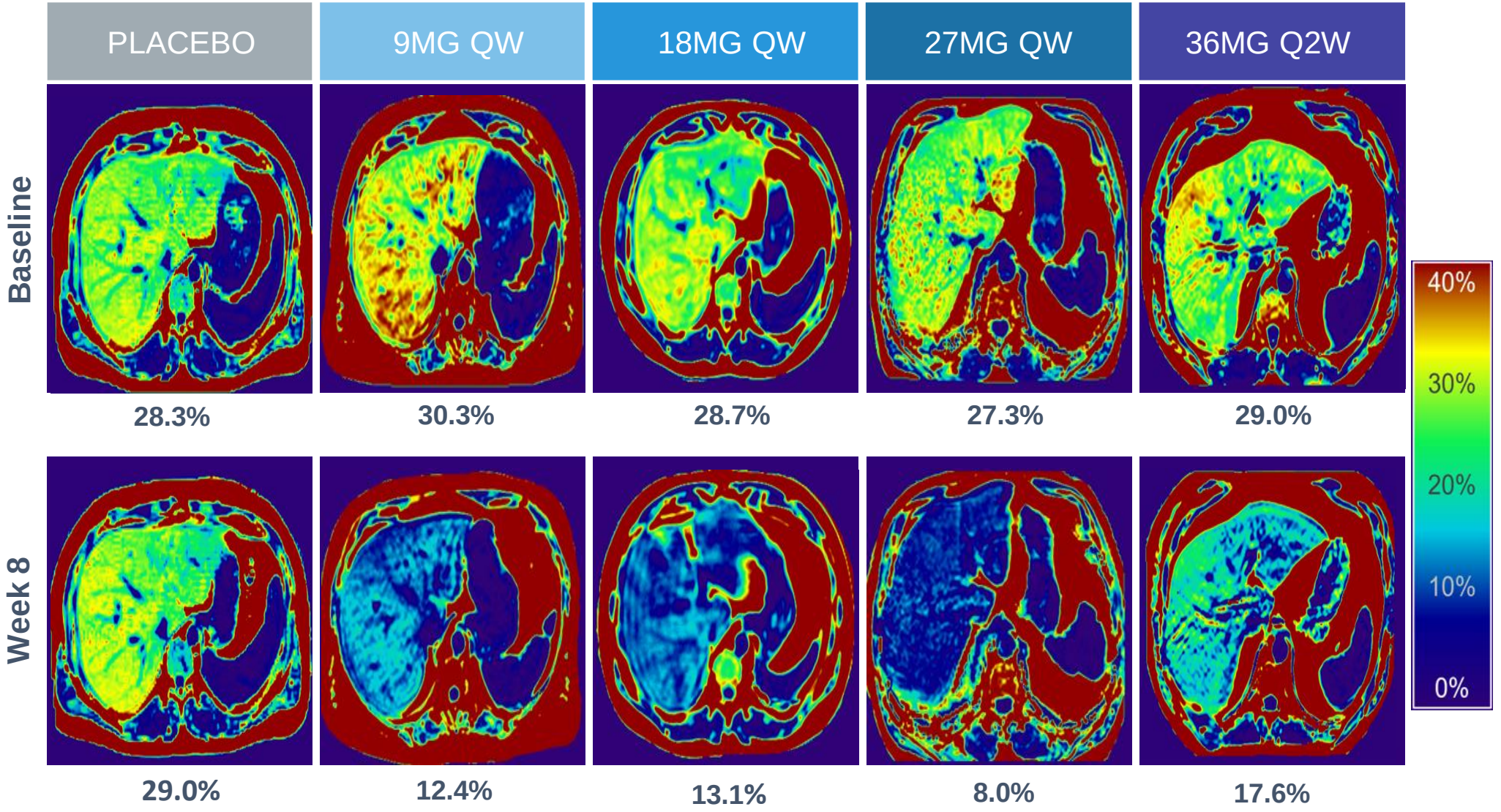


HIGH RESPONDER RATES

- **≥ 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 versus placebo

Representative MRI-PDFF Imaging Demonstrating Reduction in Liver Fat After 8 Weeks of Pegozafermin Treatment



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- Though no serious adverse events related to pegozafermin were seen, further safety and tolerability data from a longer period of drug exposure at the target dose are necessary

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- Additional cardiometabolic improvements potentially make pegozafermin an attractive therapy in severe hypertriglyceridemia 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