Prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) in subjects with severe hypertriglyceridemia (SHTG): Baseline data from the pegozafermin ENTRUST Phase 3 SHTG Trial

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BACKGROUND

- Severe hypertriglyceridemia (SHTG), defined as TG ≥ 500mg/dL, impacts roughly 3 million adults with a higher prevalence observed in individuals with metabolic co-morbidities such as obesity, diabetes, chronic kidney disease, atherosclerotic cardiovascular disease, and metabolic dysfunction-associated steatotic liver disease (MASLD).[1,2]
- To date, the estimated prevalence of MASLD in patients with SHTG ranges between 67% (based on claims data) and up to 100% in clinical trial data.[3-5]
- However, it remains unclear whether these patients had simple steatosis or more advanced disease such as metabolic dysfunction-associated steatohepatitis (MASH) which can include fibrosis.
- Pegozafermin, a FGF21 analog, is being studied in a Phase 3 randomized controlled trial in SHTG subjects (ENTRUST trial) in which a large subset of patients had baseline assessments for liver fat, some of which also had liver stiffness measurements.

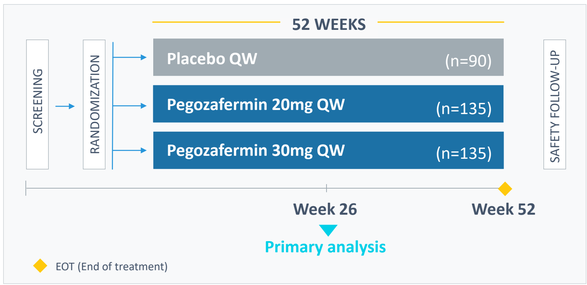
[1]*Circulation* Volume 140, Number Suppl_1: Abstract 14745;[2]*J Clin Lipidology* 2023;17(6):777-787;[3]*JACC Adv.* 2024; May, 3 (5). https://doi.org/10.1016/j.jacadv.2024.100932;[4]*Nat Med* 2023; 29:1782-1792;[5]*Proceedings* 2022;80(1):6 Keynote poster abstract 2.4.

OBJECTIVE

- To assess the blinded baseline prevalence of MASLD and MASH in a subset of SHTG patients participating in the ENTRUST trial, using hepatic steatosis ≥ 5% and liver stiffness measurements ≥ 7.5kPa indicative of fatty liver and fibrosis ≥ F2, respectively.

METHODS

ENTRUST Trial Design: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study



KEY INCLUSION CRITERIA

- TG ≥ 500mg/dL and ≤ 2,000mg/dL
- Stable background lipid modifying therapy

PRIMARY ENDPOINT

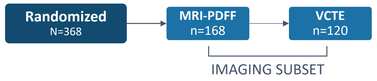
- Percent change from baseline in fasting TGs at Week 26 vs. placebo

KEY SECONDARY ENDPOINTS

- Liver fat by MRI-PDFF, Various lipids, HbA1c at Week 26 vs. placebo, TGs at Week 52 vs. placebo

METHODS (CONT'D)

ENTRUST Patient Disposition for Imaging



ENTRUST MRI-PDFF and VCTE Subset

- This analysis evaluates the baseline prevalence of hepatic steatosis (MRI-PDFF) and liver stiffness (VCTE) in SHTG patients participating in ENTRUST.
- Screening period:
  - Screening stabilization period: At least 4 weeks for medication, diet and exercise
  - TG qualification period: Mean of two (or three) fasting TGs at least a week apart
    - Up to 10% of subjects could qualify with a mean TG ≥ 450mg/dL (5.07mmol/L) or up to 2500mg/dL (28.25mmol/L)
- MRI-PDFF and VCTE are not requirements for the main study.
- Eligible subjects could obtain baseline MRI-PDFF and VCTE during the TG qualifying period.

RESULTS

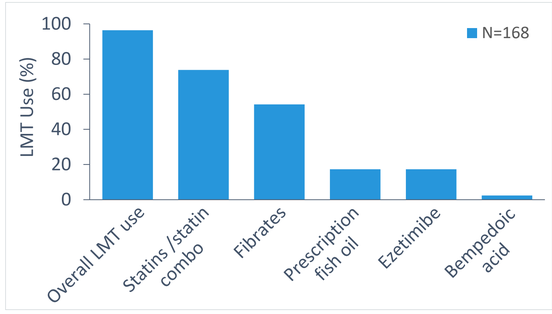
Demographics and Baseline Characteristics

PARAMETER	N=168
Age (range)	53.5 (20,80)
Male (%)	75
Race, (%)	
Asian	6.5
Black	0.6
White	90.5
American Indian/Alaskan Native	1.8
Ethnicity, (%)	
Hispanic or Latino	34.5
Not Hispanic or Latino	65.5
Diabetes (%)	56.5
Hypertension (%)	69.6
Cardiovascular Disease (%)	27.4
History of Acute Pancreatitis (%)	13.1
MASLD* (%) [self-reported MASLD diagnosis]	10.7
Qualifying Mean Triglyceride (mg/dL)	
Median	750
IQR limits	546, 1059
BMI (kg/m², SD)	31.4 (4.8)
LDL (mg/dL, SD)	74.2 (36.8)
HDL-C (mg/dL, SD)	28.7 (8.8)
Total Cholesterol (mg/dL, SD)	224.3 (56.6)
ALT (U/L, SD)	31.3 (19.6)
PDFF (%, SD)	15.7 (9.0)
VCTE (kPa, SD)	7.9 (7.3)

Population = Randomized analysis set with evaluable MRI-PDFF baseline data.
Baseline characteristics are comparable to the overall randomized population at the time of data cut-off.
*NAFLD nomenclature has been redefined as MASLD.

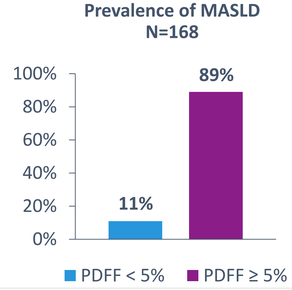
RESULTS (CONT'D)

Concomitant Lipid Modifying Therapy Use



Subjects may be on more than one lipid-modifying therapy.
Population = Randomized analysis set with evaluable MRI-PDFF baseline data.
Incretin use was 13%.

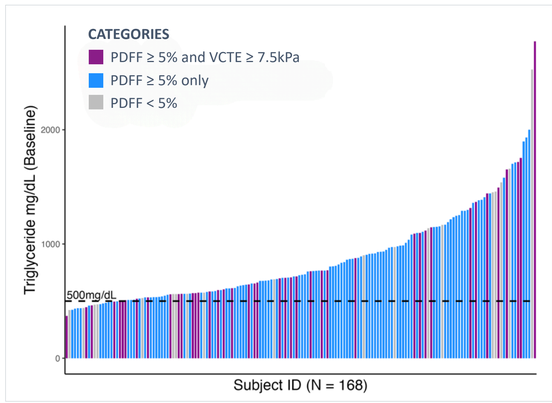
High Prevalence of MASLD in Patients with SHTG



- Per medical history, less than 11% of subjects had a preexisting diagnosis of MASLD.
- A significant number of SHTG subjects have undiagnosed liver disease.

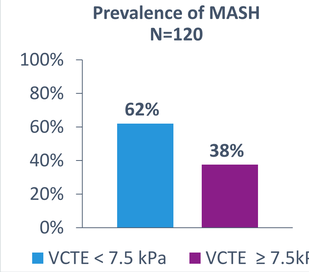
Population = Randomized analysis set with evaluable MRI-PDFF baseline data.

Baseline Triglyceride Waterfall Plot (MRI-PDFF Set)



Population = Randomized analysis set with evaluable MRI-PDFF baseline data.

High Prevalence of MASH in Patients with SHTG



- Liver stiffness measurements of ≥ 7.5kPa are indicative of stage 2 fibrosis.*
- Over 1/3 of subjects in this study are at risk for significant fibrosis.

Population = Randomized analysis set with evaluable MRI-PDFF and VCTE baseline data.
*Fibrosis stages in MASH range from F0 (no fibrosis)-F4 (cirrhosis). F2 denotes moderate scarring with thickening scar tissue.

Baseline Triglyceride Waterfall Plot (VCTE Set)

Population = Randomized analysis set with evaluable MRI-PDFF and VCTE baseline data.

CONCLUSION

- These data suggest SHTG subjects have a high prevalence of clinically meaningful hepatic steatosis (89%).
- Approximately 1/3 of these patients also had liver stiffness measurements consistent with significant fibrosis (≥ F2).
- Presence of hepatic steatosis and liver stiffness occurred across the entire range of baseline TG levels, suggesting a high risk of liver disease in SHTG patients.
- These baseline findings in ENTRUST corroborate baseline data from the ENTRIGUE trial suggesting routine assessment of hepatic steatosis may be warranted in SHTG patients.

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