

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 $\geq 500\text{mg/dL}$, 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.

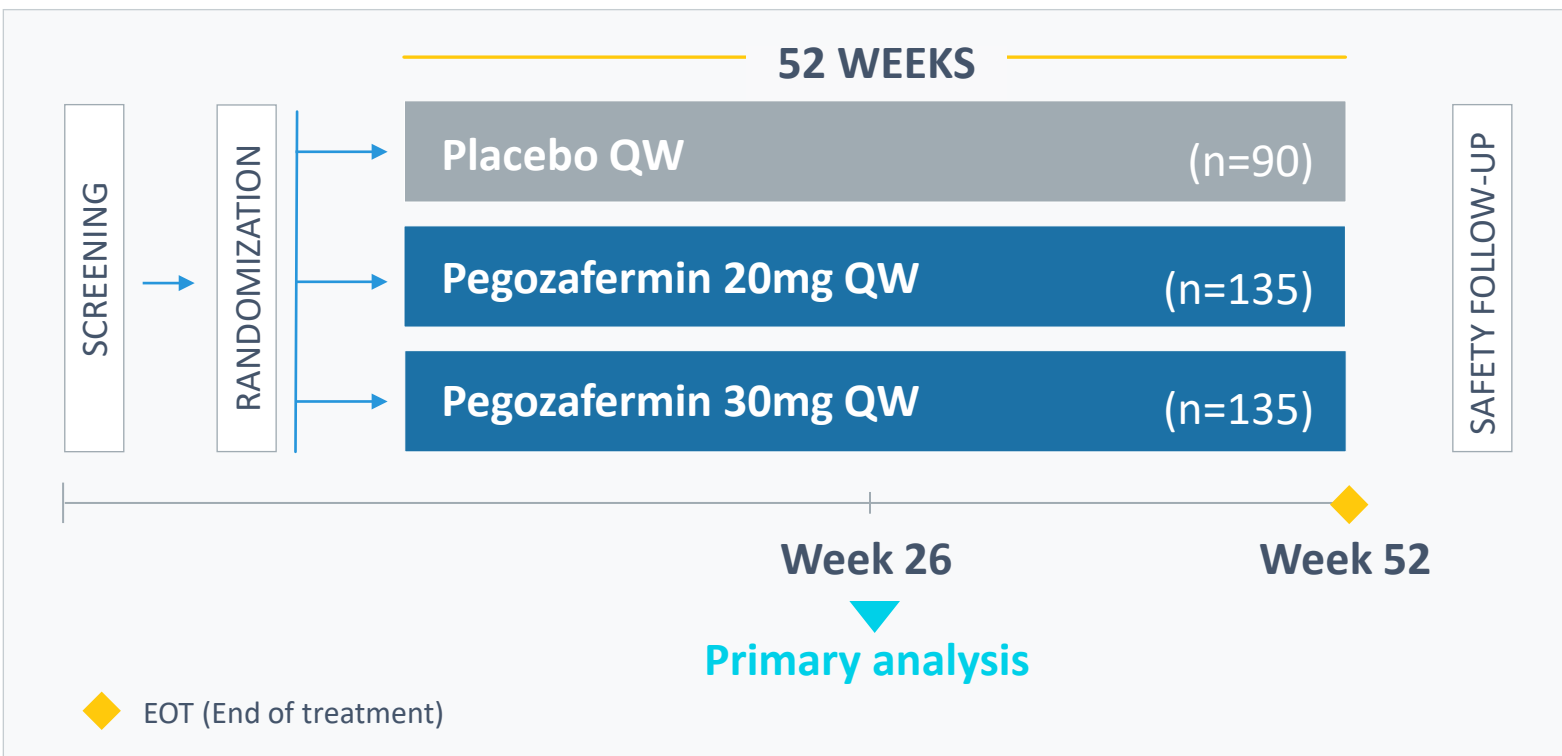
¹Circulation Volume 140, Number Suppl. 1: Abstract 14745; ²J Clin Lipidology 2023;17(6):777-787; ³JACC Adv. 2024; May, 3 (5). <https://doi.org/10.1016/j.jacadv.2024.100932>; ⁴Nat Med 2023; 29:1782-1792; ⁵Proceedings 2022;80(1):6 Keynote poster abstract 2.4.

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 $\geq 5\%$ and liver stiffness measurements $\geq 7.5\text{kPa}$ indicative of fatty liver and fibrosis $\geq \text{F2}$, respectively.

METHODS

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



KEY INCLUSION CRITERIA

- TG $\geq 500\text{mg/dL}$ and $\leq 2,000\text{mg/dL}$
- Stable background lipid modifying therapy

KEY SECONDARY ENDPOINTS

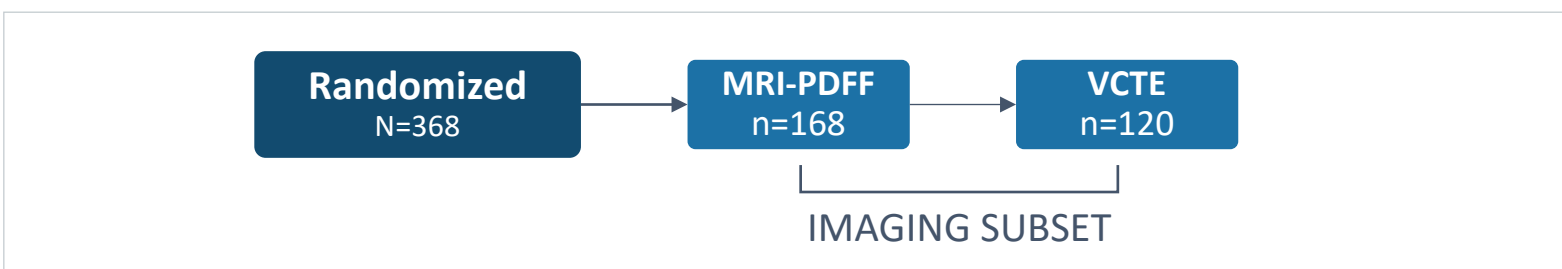
- Liver fat by MRI-PDFF, Various lipids, HbA1c at Week 26 vs. placebo, TGs at Week 52 vs. placebo

PRIMARY ENDPOINT

- Percent change from baseline in fasting TGs at Week 26 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 $\geq 450\text{mg/dL}$ (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

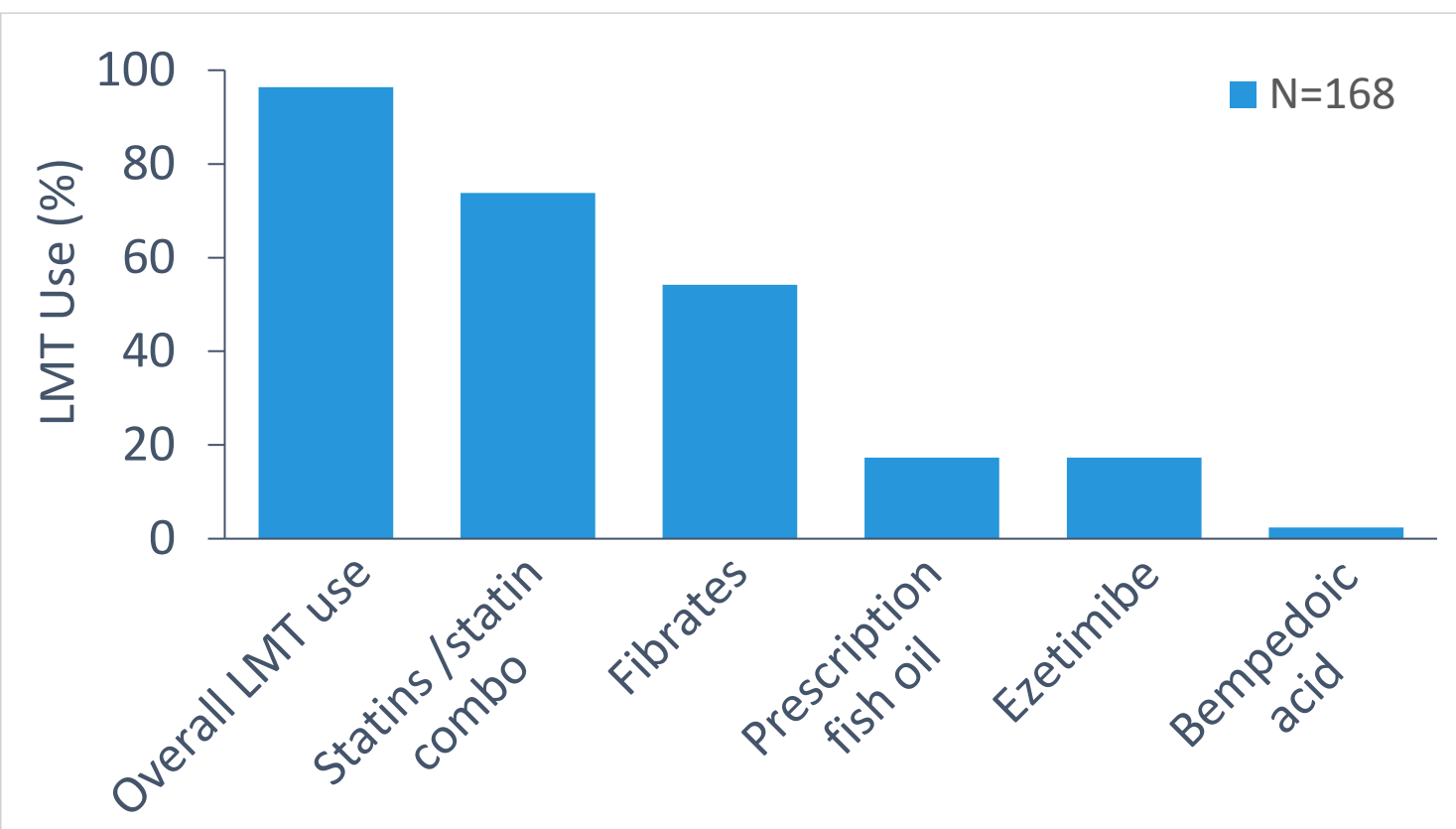
PARAMETER	N=168
Age (range)	53.5 (20,80)
Male (%)	75
Race, (%)	
Asian	6.5
Black	0.6
White	90.5
American Indian/Alaskan Native	1.8
Ethnicity, (%)	
Hispanic or Latino	34.5
Not Hispanic or Latino	65.5
Diabetes (%)	56.5
Hypertension (%)	69.6
Cardiovascular Disease (%)	27.4
History of Acute Pancreatitis (%)	13.1
MASLD* (%) [self-reported MASLD diagnosis]	10.7
Qualifying Mean Triglyceride (mg/dL)	
Median	750
IQR limits	546, 1059
BMI (kg/m ² , 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.

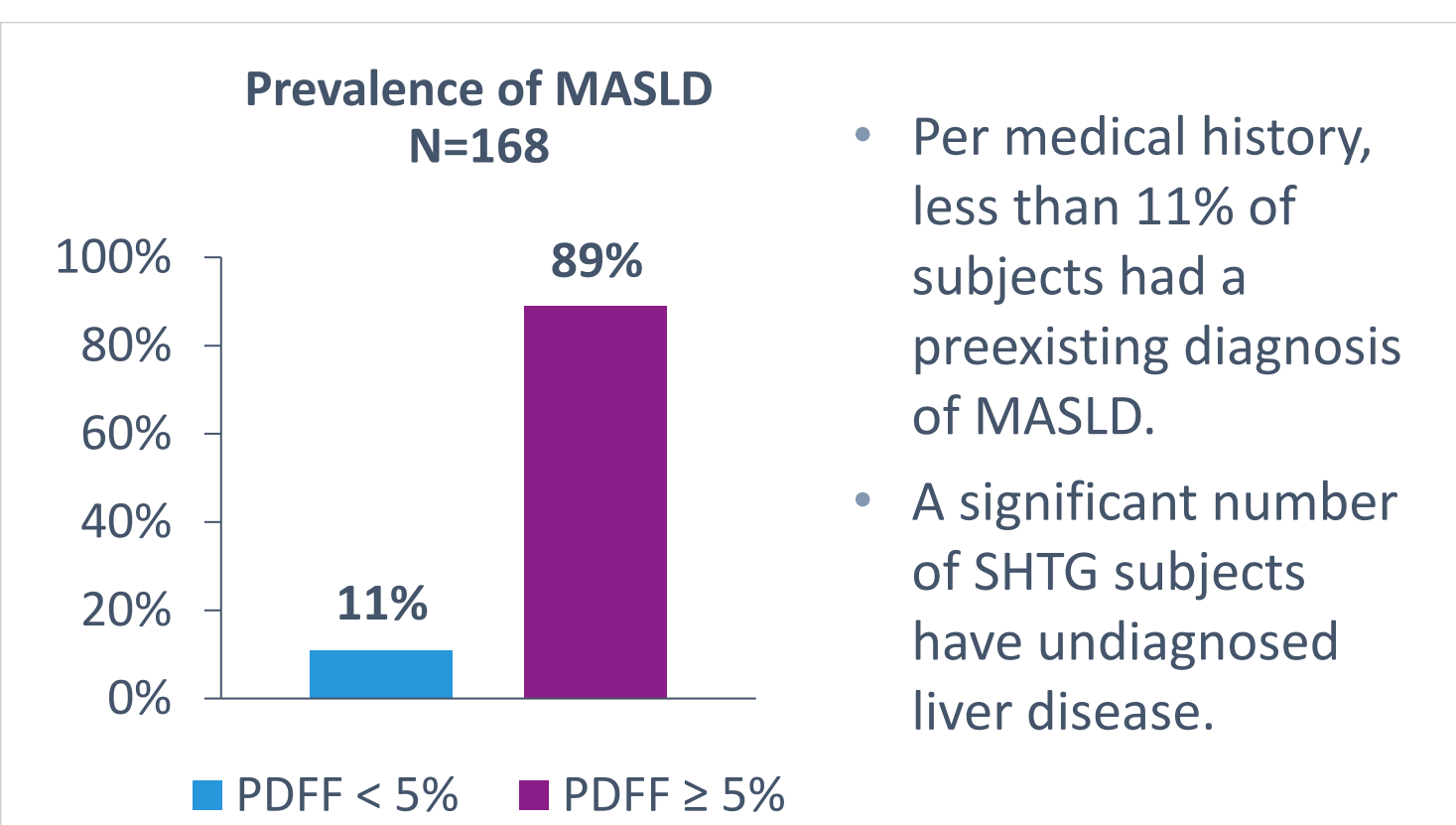
RESULTS (CONT'D)

Concomitant Lipid Modifying Therapy Use



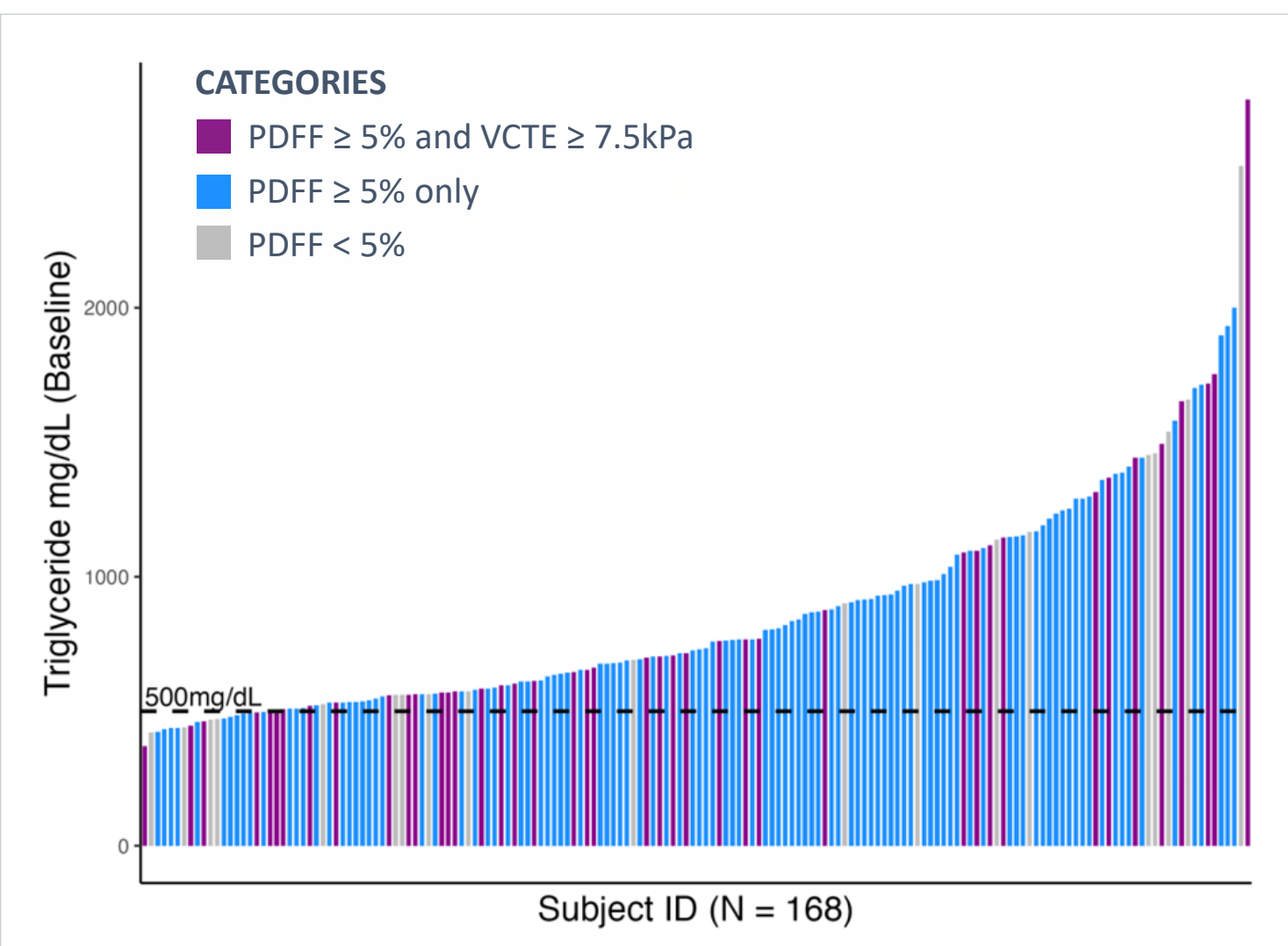
Subjects may be on more than one lipid-modifying therapy. Population = Randomized analysis set with evaluable MRI-PDFF baseline data. Incretin use was 13%.

High Prevalence of MASLD in Patients with SHTG



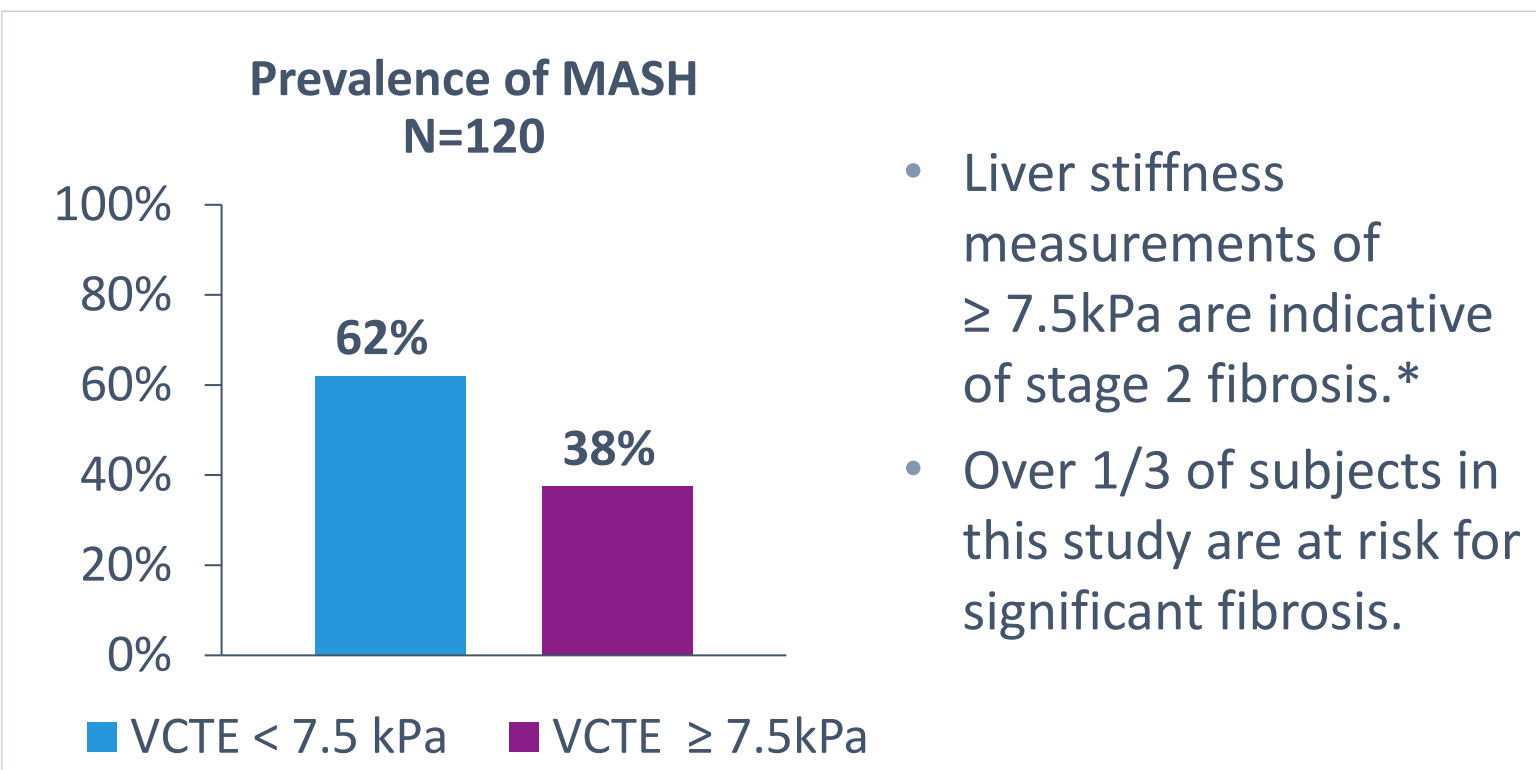
Population = Randomized analysis set with evaluable MRI-PDFF baseline data.

Baseline Triglyceride Waterfall Plot (MRI-PDFF Set)



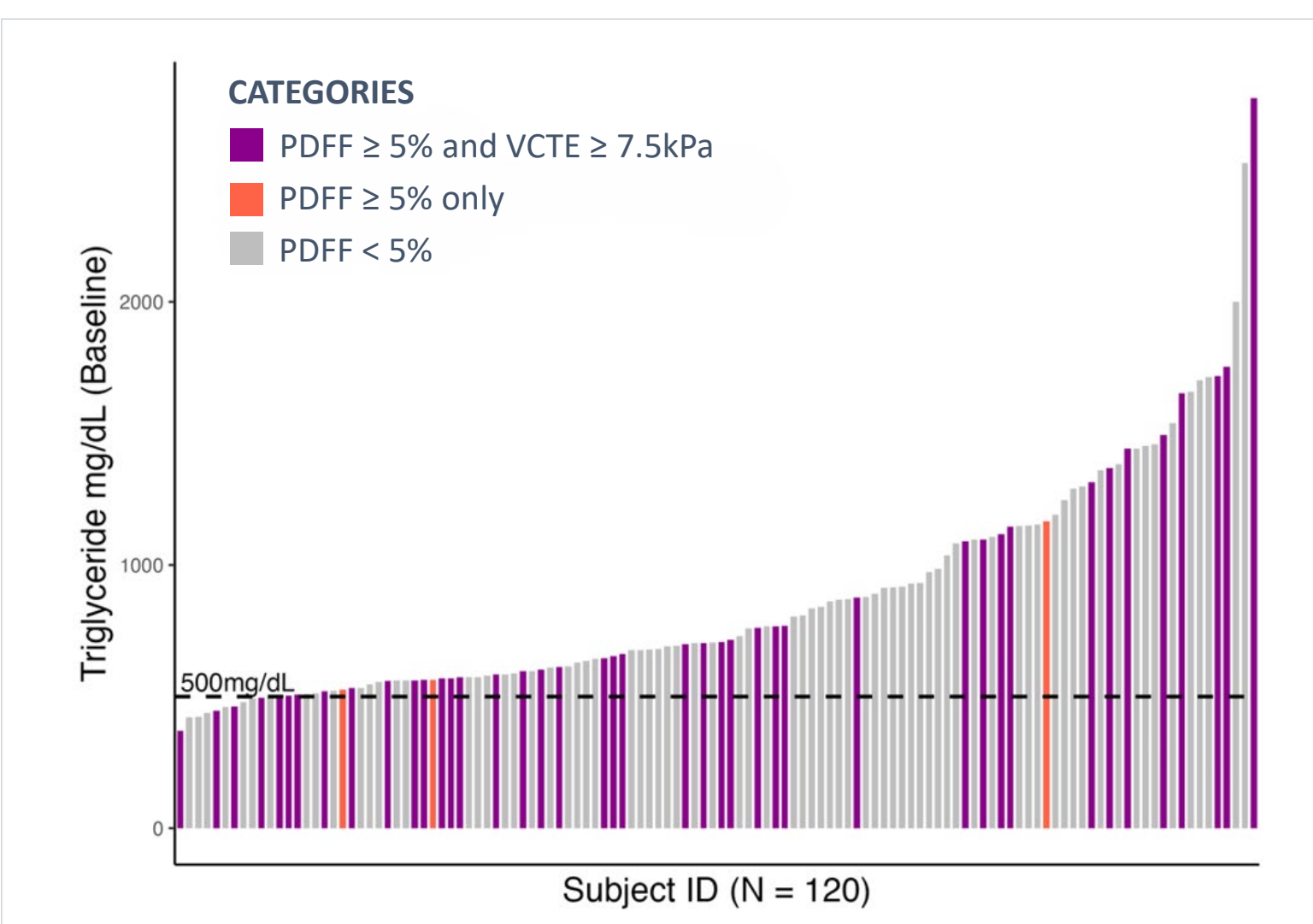
Population = Randomized analysis set with evaluable MRI-PDFF baseline data.

High Prevalence of MASH in Patients with SHTG



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 ($\geq \text{F2}$).
- 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.

ACKNOWLEDGEMENTS: Special acknowledgment to Lulu Sterling, PhD for statistical support

DISCLOSURE: Deepak Bhatt has received research funding from 89bio; Full disclosure list submitted with abstract.

