Prevalence of Nonalcoholic Fatty Liver Disease in Patients With Severe Hypertriglyceridemia (SHTG) – Initial Baseline Data From an Ongoing Phase 2 Study

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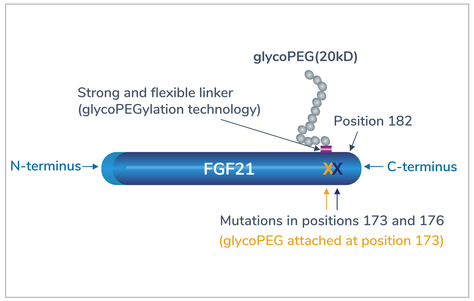
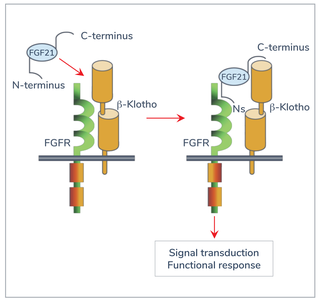
INTRODUCTION

- US prevalence of SHTG is estimated ~4 million and is commonly found in patients with insulin resistance, type 2 diabetes mellitus, obesity, and other metabolic dysregulation that also influence the development of nonalcoholic fatty liver disease (NAFLD).
- Metabolic disturbances and NAFLD appear to confer bidirectional risk on each other. NAFLD also has been associated with severity of acute pancreatitis and may play a prognostic role in acute pancreatitis, for which the SHTG population is at higher risk.
- The prevalence of NAFLD in the SHTG population has not been clearly defined in the literature.
- Fibroblast growth factor 21 (FGF21), an endogenous hormone regulates several important metabolic pathways, such as glucose homeostasis, lipid metabolism, insulin sensitivity, and ketogenesis. BIO89-100, a proprietary glycoPEGylated FGF21 analog, is currently being evaluated in ENTRIGUE, a phase 2, randomized, double-blind, placebo-controlled study to explore the efficacy and safety in subjects with severe hypertriglyceridemia.

BIO89-100, an FGF21 Analog Optimally Engineered to Balance Efficacy and Long Dosing Interval





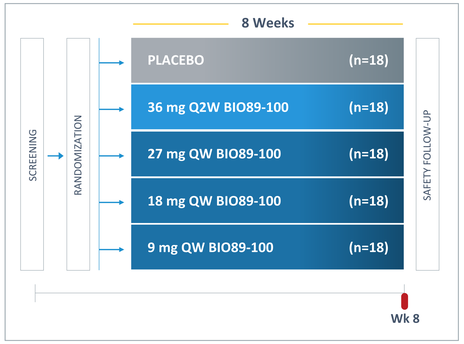
- Proprietary glycoPEGylation technology with site-specific mutations.
- Long half-life of 55-100 hours vs native FGF21 half-life of <2 hours.
- Low nanomolar potency against FGF receptors 1c, 2c, 3c, similar to native FGF21; no activity against receptor 4 (leads to increased LDL).
- Subcutaneous dosing once a week or once every 2 weeks.

OBJECTIVE

- This interim analysis aims to elucidate the baseline prevalence of hepatic steatosis in patients with SHTG and baseline MRI-PDFF who are participating in ENTRIGUE.

METHODS

ENTRIGUE – Phase 2 SHTG Trial Design



% change in TGs from baseline.
*MRI-PDFF=magnetic resonance imaging proton density fat fraction.

KEY INCLUSION CRITERIA

- TG ≥500 mg/dL and ≤2000 mg/dL.
- Background therapy of statins and/or prescription fish oil OR not on any background therapy.

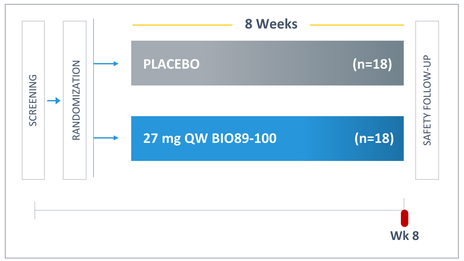
PRIMARY ENDPOINT

- % change in TGs from baseline.

KEY SECONDARY ENDPOINTS

- Other lipids and metabolic parameters.
- Liver fat*(MRI-PDFF).

ENTRIGUE – Phase 2 SHTG Fibrate Cohort Trial Design



% change in TGs from baseline.
*MRI-PDFF=magnetic resonance imaging proton density fat fraction.

ENTRIGUE was expanded to include an additional cohort of patients on fibrates

KEY INCLUSION CRITERIA

- TG ≥500 mg/dL and ≤2000 mg/dL.
- Background therapy of fibrates.
- Baseline MRI-PDFF of ≥6%.

PRIMARY ENDPOINT

- % change in TGs from baseline.

KEY SECONDARY ENDPOINTS

- Other lipids and metabolic parameters.
- Liver fat*(MRI-PDFF).

- Screening period:
  - Lifestyle stabilization period: 4 weeks, or 6 weeks for subjects for washout of medications.
  - Qualification period: Mean of two (or three) fasting TGs must be 500 mg/dL-2000 mg/dL. (up to 10% of subjects may qualify with an average TG of 475-499 mg/dL).
- Sites with MRI capabilities can obtain a baseline MRI-PDFF in consenting subjects during the TG qualifying period.
- MRI-PDFF is not a requirement for the main study.
- ENTRIGUE MRI-PDFF sub-study will assess baseline prevalence of hepatic steatosis in all SHTG patients who undergo baseline MRI-PDFF.

RESULTS

Demographics and Baseline Characteristics

PARAMETER	MRI-PDFF N=14
Age (range)	57 (40-70)
Female	42.9
Male	57.1
Race, (%)	
Asian	0
Black	0
White	100
Not Reported	0
Ethnicity, (%)	
Hispanic or Latino	28.6
Not Hispanic or Latino	71.4
Waist Circumference (mean, cm)	111.3
BMI (mean, kg/m²)	34.5
Qualifying Mean Triglyceride (mg/dL)	
Mean	665
Min, Max	495, 1054

PARAMETER	MRI-PDFF N=14
MRI-PDFF (mean, % liver fat)	20.1
Min, Max	6.2, 39.2
Statin Use (%)	35.7
Prescription Fish Oil (%)	7.1
Washout of Niacin or Fibrate (%)	21.4
LDL (mg/dL)	
Mean (range)	101 (46-166)
HDL (mg/dL)	
Mean (range)	28 (22- 39)
HOMA-IR (mean)	
Mean (range)	10.3 (3.1-26.4)
ADIPO-IR (mean)	
Mean (range)	17.7 (6.9-33.7)

Baseline characteristics are comparable to the overall randomized population at the time of data cut-off.

Subjects With MRI-PDFF Data

SUBJECTS	QUALIFYING MEAN TG (mg/dL)	TG (mg/dL) MRI-PDFF	T2DM
1	561	39.2	No
2	495	29.8	No
3	1054	29.0	No
4	639	28.9	No
5	864	28.7	No
6	499	23.4	No
7	556	21.9	Yes
8	776	21.4	Yes
9	862	15.4	No
10	515	13.2	Yes
11	591	9.6	No
12	699	7.5	No
13	540	7.3	No
14	*468	6.2	Yes
Mean	665	20.1	28.5%

*Screen fail

CONCLUSIONS

- In this initial look at the ongoing ENTRIGUE study, all subjects with baseline MRI-PDFF showed clinically meaningful hepatic steatosis (MRI-PDFF ≥5%), with liver fat content ranging from 6.2 to 39.2%.
- The prevalence and severity of hepatic steatosis was greater than expected.
- Baseline MRI-PDFF values did not correlate with baseline TG values.
- Given the potential broad metabolic benefits of BIO89-100, it will be important to better understand the correlation between NAFLD and the risk of acute pancreatitis and to explore the potential benefit that liver fat reduction may have in patients with SHTG.
- These initial baseline findings in ENTRIGUE suggest that routine assessment of hepatic steatosis may be warranted in SHTG patients.