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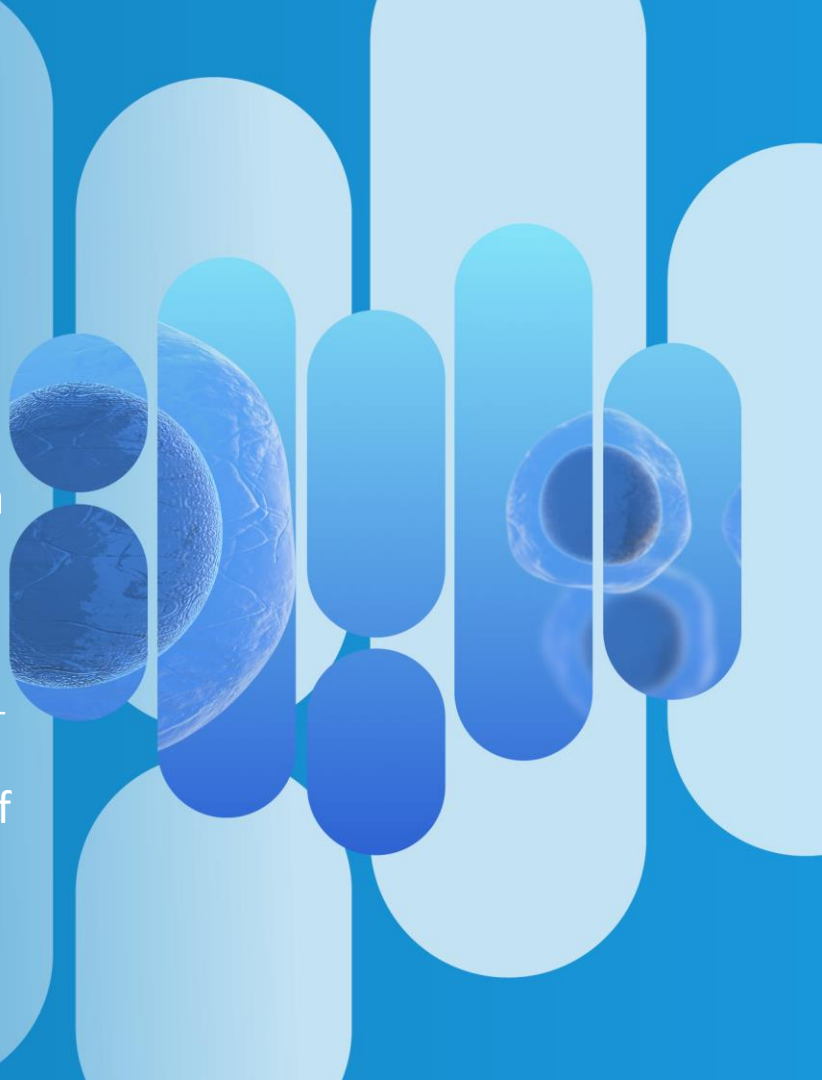
ABSTRACT

Prevalence of NAFLD in Subjects with Severe Hypertriglyceridemia: Initial Baseline Data from an Ongoing Phase 2 Study

ENtrigue

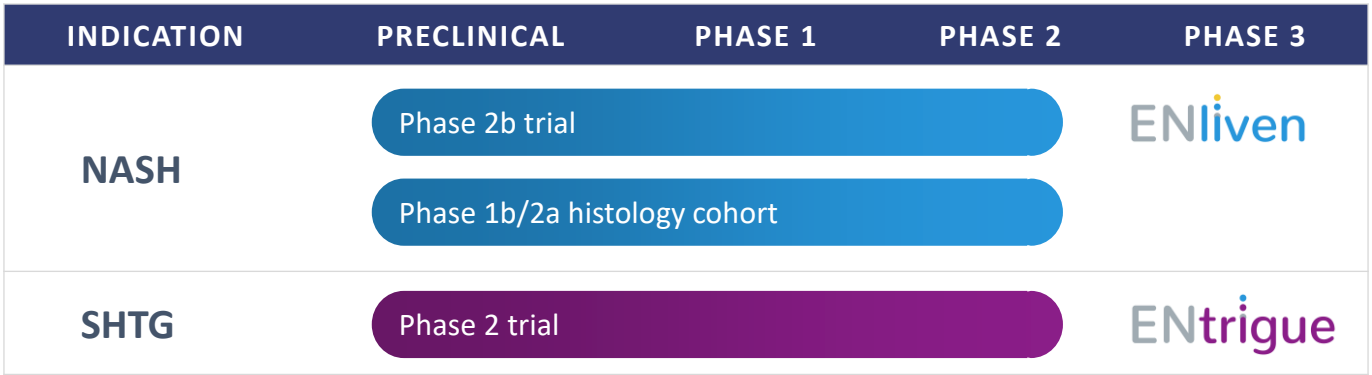
A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Explore the Efficacy and Safety of BIO89-100 in Subjects with Severe Hypertriglyceridemia

Protocol Number: BIO89-100-221

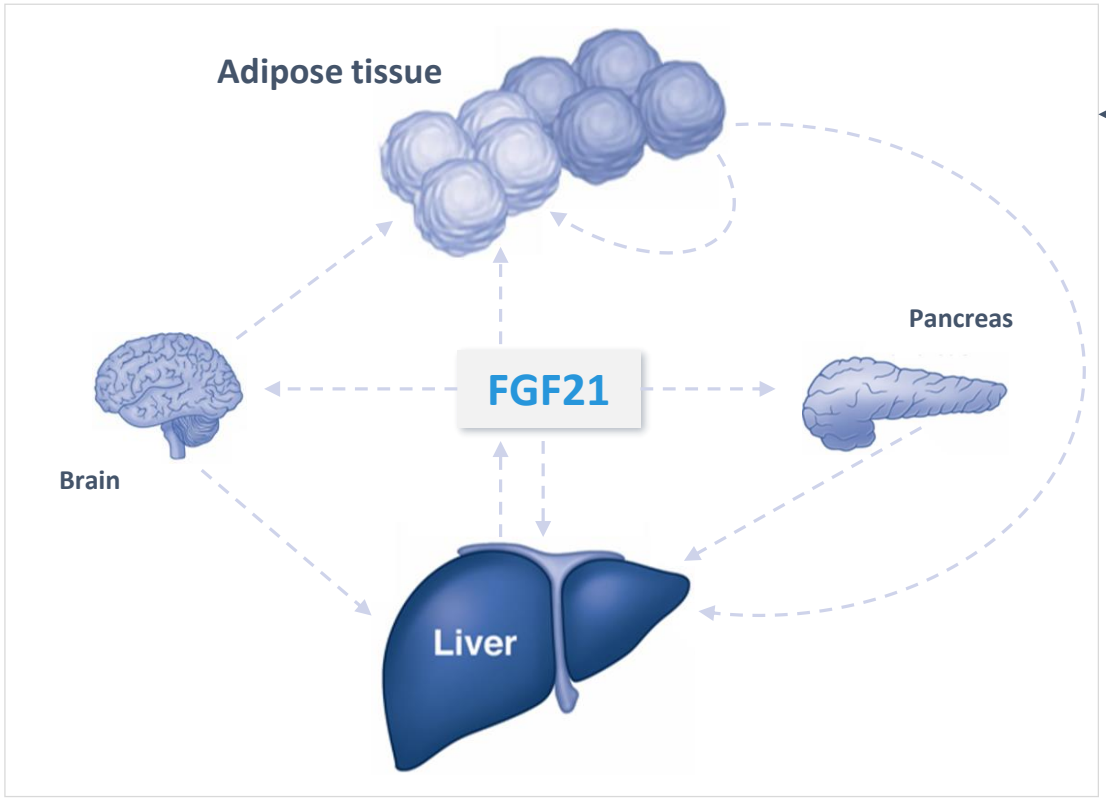


Introduction

- 89bio is a clinical-stage biopharmaceutical company focused on development and commercialization of innovative therapies for the treatment of liver and cardio-metabolic diseases
- The lead product candidate, BIO89-100, is a proprietary FGF21 analog being developed for the treatment of nonalcoholic steatohepatitis (NASH) and severe hypertriglyceridemia (SHTG)



FGF21 is an Endogenous Hormone with Broad Reaching Effects Across Multiple Organs



FGF21 can act directly or indirectly on target organs

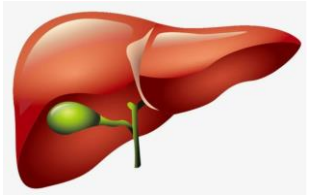
FGF21-related organ cross talk can be mediated by:

- Upstream regulators that induce FGF21, such as nutritional stress or transcription factors
- Downstream regulators, such as adiponectin

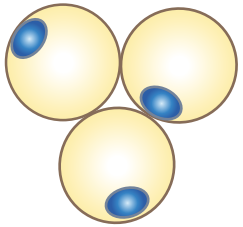
Zhang F et al. Mol Endocrinol 2015;29(10):1400-1413

FGF21 regulates energy expenditure and glucose and lipid metabolism

- ↑ Lipid disposal
- ↑ HDL synthesis
- ↓ TG synthesis
- ↓ LDL synthesis
- ↓ De novo lipogenesis
- ↑ Insulin sensitivity
- ↓ Fibrosis
- ↓ Inflammation



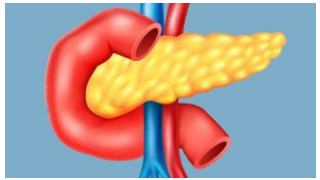
White adipose tissue



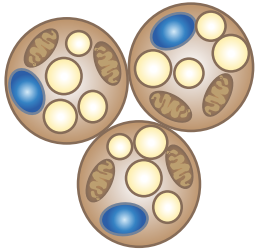
- ↑ Adiponectin production
- ↑ TG disposal
- ↑ FGF21 production
- ↑ Insulin signaling
- ↓ Inflammation

FGF21

- ↑ β cell survival
- ↑ β cell function
- ↓ GH signaling
- ↓ Glucagon



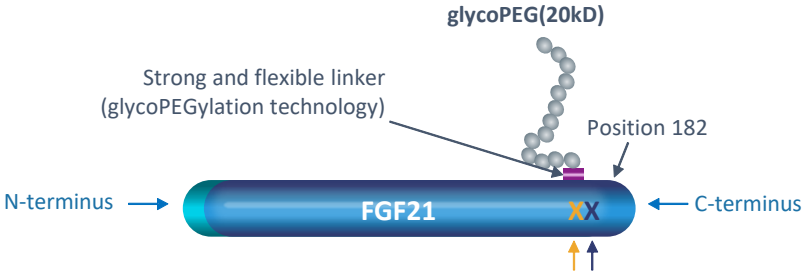
Brown adipose tissue

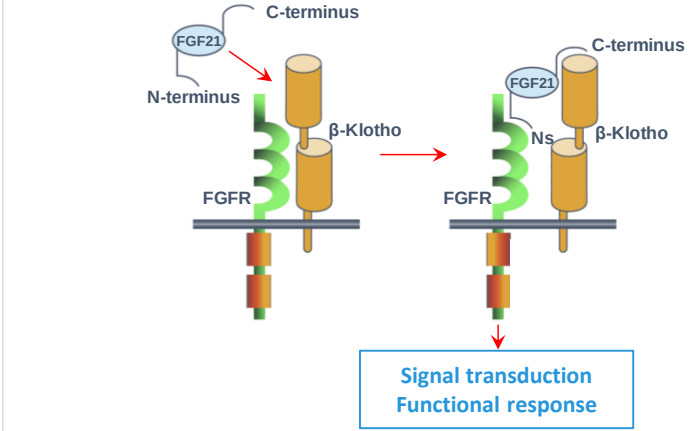


- ↑ Glucose Uptake
- ↑ TG disposal
- ↑ Thermogenesis

1. Bondurant LD, et al. *Cell Metab*. 2017;25(4):935-944.e4.
2. Schlein C, Talukdar S, Heine M, et al. *Cell Metab*. 2016;23(3):441-4553.
3. Yen CLE, et al. *J Lipid Research.2008;*49,(11): 2283-301.
4. Fisher FM, et al. *Genes Dev*. 2012;26(3):271–281.
5. Xu J, et al. *Diabetes*. 2009;58(1):250-259
6. Holland et al, *Cell Metab*. 2013 May 7;17(5):790-7.
7. Vandanmagsar, B., et al., *Cell reports 2015. 15*(8), 1686–1699.

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

Phase 1b/2a NASH Trial Design

MRI-PDFF

- Placebo (n=19) combined across cohorts for analysis
- Randomized, pharmacodynamic (PD) and safety analysis set n=81; Study completers n=71
- MRI analysis set n=75 (patients with post-baseline MRI)

KEY INCLUSION CRITERIA

- NASH* or phenotypic NASH (PNASH)#
- PDFF≥10%

*Patients with biopsy-proven F1-3

#Central obesity plus T2DM or evidence of liver injury

KEY TRIAL ENDPOINTS

- Safety, PK
- Relative changes in liver fat
- Serum lipids, liver and metabolic markers

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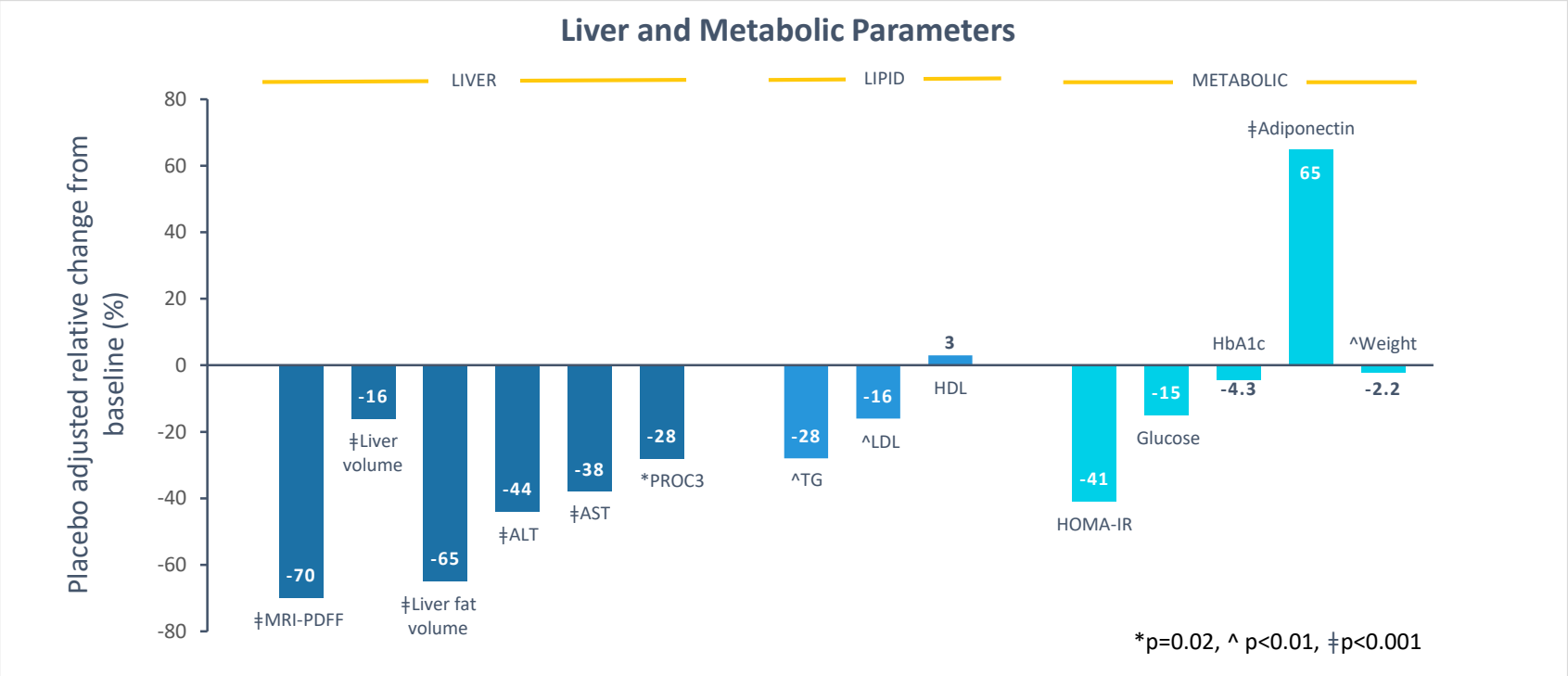
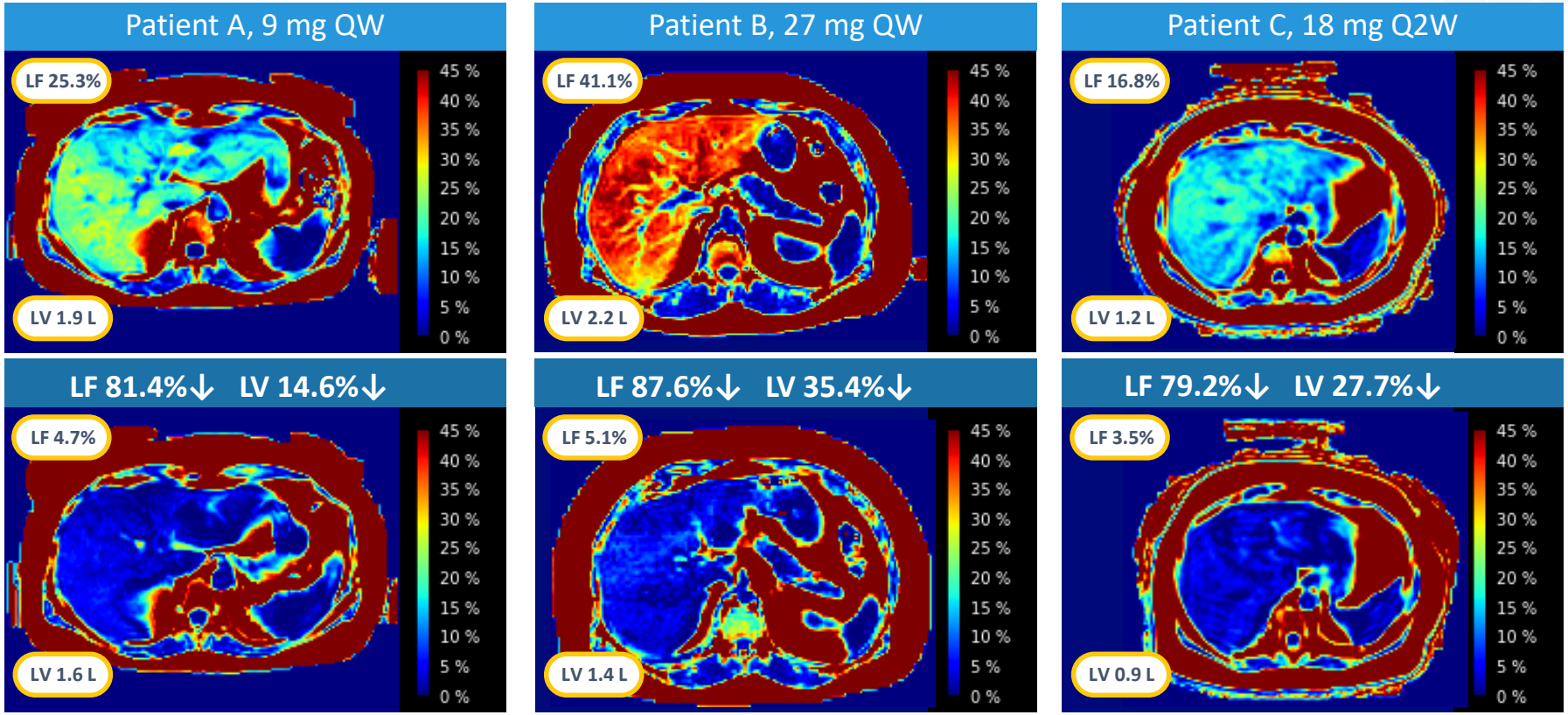
BIO89-100 27 mg QW demonstrated favorable effects on liver fat, lipids and glycemic control parameters



There were no drug-related serious adverse events, hypersensitivity reactions or adverse effects on blood pressure or heart rate reported. Treatment was associated with a favorable safety and tolerability profile. The most common AE was increased appetite (without weight gain), while GI-related AEs did not differ from placebo.

Substantial Reduction in Liver Fat and Liver Volume Across Dose Groups



Severe Hypertriglyceridemia (SHTG) and Prevalence of Nonalcoholic Fatty Liver Disease (NAFLD)

US prevalence with SHTG estimated ~ 4 million

Commonly found in patients with insulin resistance, T2DM, obesity, and other metabolic dysregulation which also influence development of NAFLD

Severe and very severe TGs increase the risk of acute pancreatitis

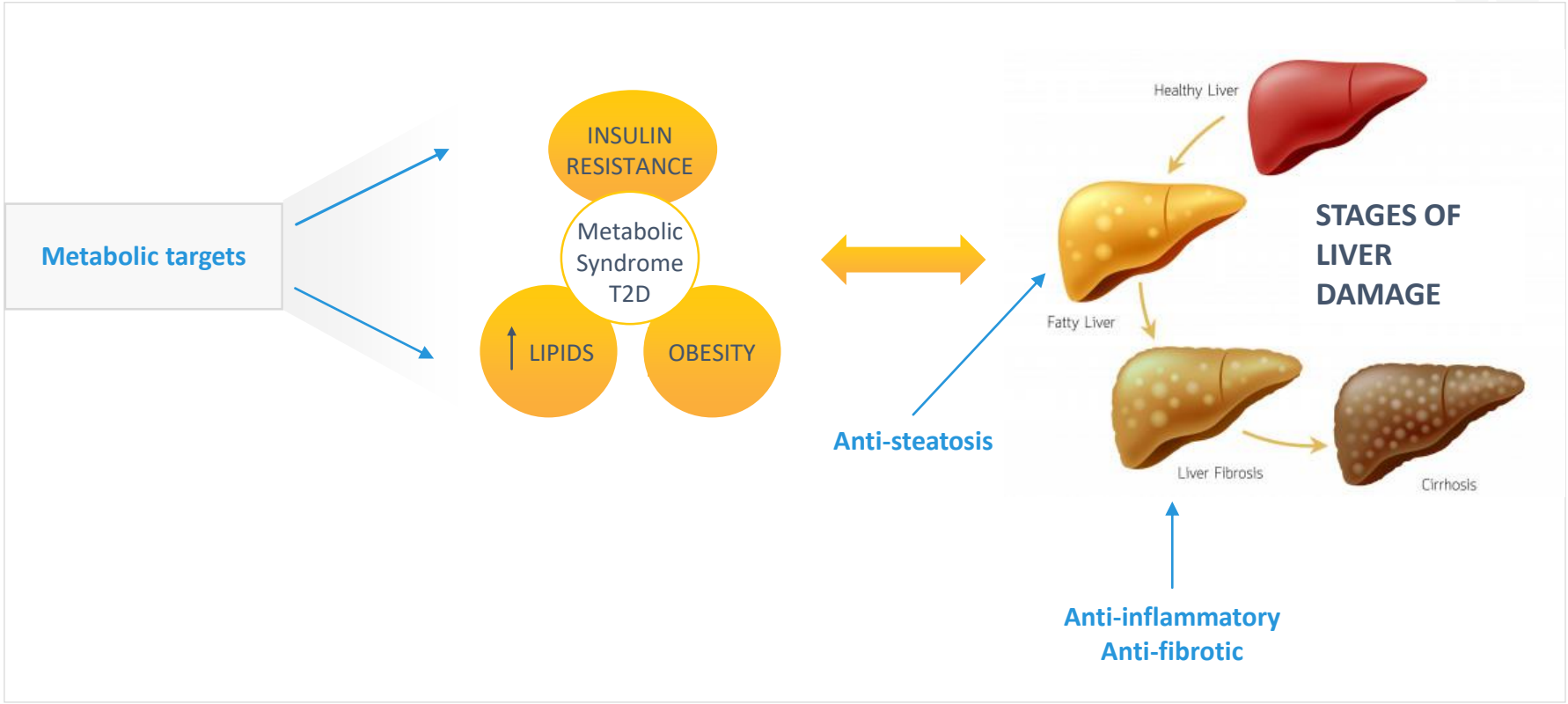
Fatty liver has been associated with the severity of acute pancreatitis and may play a prognostic role in acute pancreatitis[1,2]

Overall prevalence of NAFLD in the SHTG population has been estimated but not clearly defined in the literature

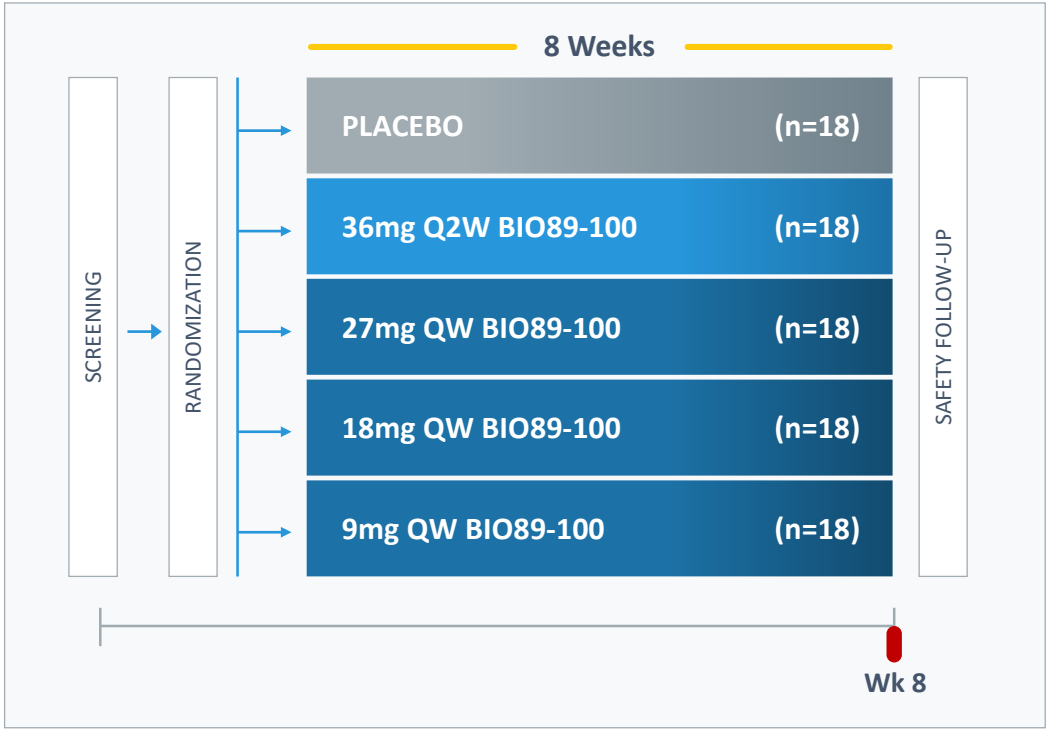
Physicians estimate that ~50% of their SHTG patients have fatty liver disease

1. Yoon SB et al.*Gastroenterol Res Pract* 2017;2017:4532320
2. Hou S et al. *Int J Surg* 2019;65:147-153

BIO89-100 targets important metabolic parameters associated with both Metabolic Syndrome and NAFLD/NASH



ENTRIGUE – Phase 2 SHTG Trial Design



% Chg in TGs from baseline

*MRI-PDFF -magnetic resonance imaging proton density fat fraction

KEY INCLUSION CRITERIA

- TG ≥500 mg/dL and ≤2,000 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 MRI-PDFF Sub-study

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

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)	MRI-PDFF % liver fat	LDL (mg/dL)	HDL (mg/dL)	T2DM	WAIST CIRCUMFERENCE (CM)	BMI (kg/m²)
1	**561**	**39.2**	162	24	No	127	NA
2	**495**	**29.8**	148	37.5	No	109	33.6
3	**1054**	**29.0**	110	25	No	122	40.1
4	**639**	**28.9**	112	29	No	97	28.3
5	**864**	**28.7**	70	25	No	99	25.4
6	**499**	**23.4**	78	22	No	122	39.8
7	**556**	**21.9**	57	30	Yes	116	34.1
8	**776**	**21.4**	46	23	Yes	116	38.3
9	**862**	**15.4**	64	23	No	103	36.2
10	**515**	**13.2**	94	26	Yes	97	27.9
11	**591**	**9.6**	167	39	No	118	39.5
12	**699**	**7.5**	105	35	No	114	32.9
13	**540**	**7.3**	64	26	No	107	31.2
14	***468**	**6.2**	135	24	Yes	NA	NA
Mean	**665**	**20.1**	**101**	**28**	**28.5%**	**111.3**	**34.5**

* Screen fail

Conclusion

- 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

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