Twelve-week treatment with BOS-580, a novel, long-acting Fc-FGF-21 fusion protein, leads to a reduction in biomarkers of liver steatosis, liver injury, and fibrosis in patients with phenotypic NASH: A randomized, blinded, placebo-controlled Phase 2A trial

ROHIT LOOMBA[1], KRIS KOWDLEY[2], JOSE RODRIGUEZ[3], NOMITA J. KIM[4], ALINA MARIA ALVAREZ[5], LINDA MORROW[6], PHILIP YIN[7,*], LAKSHMI AMARAVADI[7,†], BRENDA JEGLINSKI[7], ALICIA CLAWSON[7], SWAPAN CHOWDHURY[7], CRAIG BASSON[7,‡], ETIENNE DUMONT[7], ERIC SVENSSON[7], TATJANA ODRLJIN[7]

[1]NAFLD Research Center University of California at San Diego, La Jolla, USA. [2]Liver Institute Northwest, Seattle, USA. [3]Southwest General Healthcare Center, Fort Myers, USA. [4]Accelemed Research, Austin, USA. [5]Century Research LLC. Miami, USA. [6]Prosciento. Inc, Chula Vista, USA. [7]Boston Pharmaceuticals, Cambridge, USA.
Current affiliations: *Pemi River Health LLC, Boston, USA. †Consultant, Boston, USA. ‡Bitterroot Bio, Palo Alto, USA.

INTRODUCTION

Fibroblast growth factor 21 (FGF21) regulates energy balance and glucose and lipid homeostasis through a heterodimeric receptor complex comprising specific FGF receptors and β-Klotho.[1]

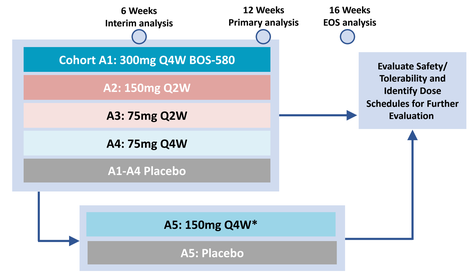
BOS-580 is an investigational, genetically engineered analog of human FGF21 fused at its N-terminus to the Fc fragment of human immunoglobulin G1 (IgG1), stabilized via the introduction of novel disulfide bonds, and uniquely manufactured from a CHO cell line generating proper glycosylation, resulting in an extended half-life that allows for once monthly dosing.[2]

BOS-580 has previously been shown in clinical trials to significantly reduce hepatic fat as well as improve biomarkers of glucose and lipid metabolism in obese, mildly hypertriglyceridemic patients after receiving 3 monthly doses of 300mg. Gastrointestinal AEs were mild to moderate and rarely led to discontinuations.[2]

AIM

To evaluate the safety, tolerability and dose-response relationship on exploratory endpoints associated with NASH pathology, in patients at high-risk of NASH (phenotypic NASH) with biweekly or once monthly subcutaneous dosing of BOS-580 over 12 weeks, in order to identify the dose levels and regimens for further development.

STUDY DESIGN & METHODS (NCT04880031)



*30mg the first month, followed by 150mg Q4W for the following months or 150mg Q4W (150mg/ mo) or PB for the total 12 week treatment period

Randomization
n=75, 4:1

Key Inclusion Criteria
- BMI 30-45 kg/m2
- Liver Fat MRI-PDFF ≥ 10%
- AST> 20 IU/L
- LSM 7.0-9.9 kPA

Exploratory Objectives
Key efficacy biomarkers
- Liver fat (MRI-PDFF)
- Liver injury (ALT, AST)
- Liver fibrosis (VCTE, PRO-C3)
- Lipids (LDL-C, HDL-C, triglycerides)
- Metabolic and glycemic biomarkers (adiponectin, insulin, C-peptide, HbA1C)

- Within each cohort, patients were randomized 4:1 (BOS 580 vs PBO) with ~15 subjects per cohort
- Patients were assessed for safety and tolerability, pharmacokinetics, and most exploratory efficacy biomarkers every 2 weeks including Week 6 (mid-treatment) and Week 12 (end of treatment)/Week 16 (end of study)

Analysis data sets were:
- Enrolled = 102 (83 completed)
- Safety = 102
- Efficacy = 89 (with baseline and week 6 or week 12 MRI-PDFF)

- Statistical significance of difference to placebo at the following levels: *p<0.05, **p<0.01, ***p<0.001
- Week 12 results are shown in the figures

RESULTS

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline characteristics were well-balanced across cohorts

Parameter	Placebo (N=37)	75mg Q4W (N=8)	75mg Q2W (N=14)	150mg Q4W (N=15)	150mg Q2W (N=15)	300mg Q4W (N=13)	Overall (N=102)
Age Mean (years)	54.1	53.5	54.7	52.1	50.7	51.8	53.0
Sex (female), n(%)	38	25	71	40	47	46	44
BMI, kg/m^2: Mean	36.5	36.5	38.3	36.2	36.4	34.9	36.5
HFF, %: Mean	18.7	24	22	21	21	24	21
Liver stiffness by VCTE (Fibroscan) (kPa): Mean	8.1	8.4	8.2	8.4	8.4	8.1	8.2
AST, IU/L: Mean	29.5	43.1	38.4	29.1	35.0	33.2	33.0
Type 2 Diabetes, n (%)	43	25	57	40	47	46	44
HbA1c, %: Mean	6.26	5.95	6.75	6.05	6.06	6.37	6.26
Trigly., mmol/L: Mean	2.20	2.05	1.93	1.77	1.91	2.36	2.06
Pro-C3, ng/mL: Mean	13.8	14.5	14.2	12.6	12.9	14.2	13.7

Note: Summaries based on the Enrolled Analysis Set

SAFETY

Low discontinuation rate due to mild to moderate, transient GI events

- Treatment discontinuations due to TEAEs were 2 (5.4%) in placebo and 3 (4.6%) in treated patients
- There were 2 Serious Adverse Events, 1 in placebo and 1 in BOS-580 treated at 150mg Q2W
- No clinically significant findings on ECG, vital signs or trends in safety laboratory parameters
- No worsening of serum low density lipoprotein levels, no cases of adverse events of hypoglycemia and no cases of worsening of pre-existing biliary disease were observed

TEAEs with the highest frequency

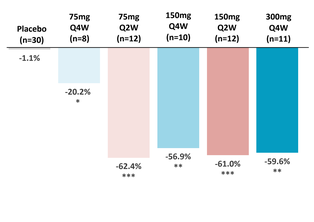
	Placebo (n=37)	75mg Q4W (n=8)	75mg Q2W (n=14)	150mg Q4W (n=15)	150mg Q2W (n=15)	300mg Q4W (n=13)
Any GI AESI Incidence	6 (16%)[a]	1 (13%)	7 (50%)	2 (13%)	6 (40%)	6 (46%)
Nausea[b]	3 (8%)	1 (13%)	5 (36%)	2 (13%)	4 (27%)	4 (31%)
Vomiting	0	0	3 (21%)	1 (7%)	4 (27%)	5 (39%)
Diarrhea	2 (5%)	0	3 (21%)	0	2 (13%)	1 (8%)
Increased Appetite[c]	0	0	5 (36%)	2 (13%)	0	4 (31%)

a Includes one patient with gastrointestinal reflux disease not summarized in the preferred term rows.
b Only 1 severe case of nausea in 150mg Q2W
c Not considered AESI

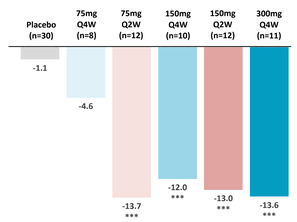
NASH BIOMARKERS

Dose dependent reduction in hepatic fat fraction as measured by MRI-PDFF

Relative Reduction in Hepatic Fat Fraction



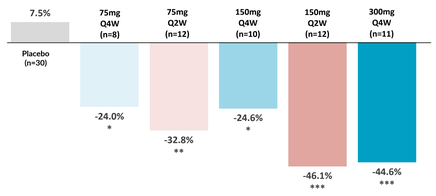
Absolute Reduction in Hepatic Fat Fraction



Based on LSmeans with treatment and baseline value effects in the model on the efficacy analysis set.

Statistically significant improvement in markers of liver injury

Relative Change in ALT

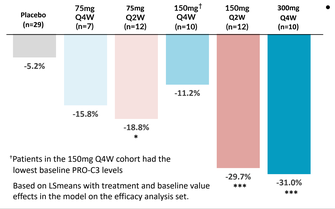


Relative Change in AST

Based on LSmeans with treatment and baseline value effects in the model on the efficacy analysis set.

Statistically significant reduction of fibrosis biomarker, PRO-C3

PRO-C3



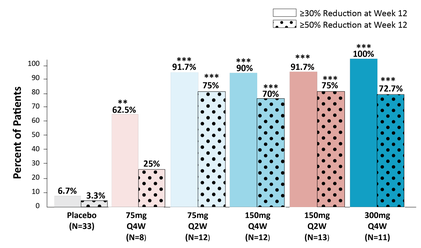
†Patients in the 150mg Q4W cohort had the lowest baseline PRO-C3 levels

Based on LSmeans with treatment and baseline value effects in the model on the efficacy analysis set.

- **Meaningful reduction in MRI-PDFF (≥30%) and PRO-C3 (>15%) was observed in 80-100% patients treated with BOS-580 vs. 22% in placebo (not shown)**

Statistically significant responder rates

Percent of Patients Achieving Meaningful Reduction in Hepatic Fat Fraction

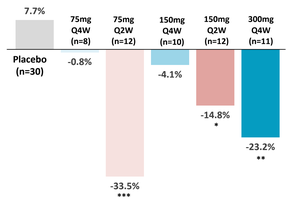


- **Liver fat normalization was achieved in 0% of patients in placebo and up to 42% in treated patients**

METABOLIC BIOMARKERS

Statistically significant improvements in serum lipid profiles

Relative Change in Triglycerides

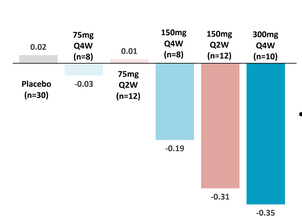


Based on LSmeans with treatment and baseline value effects in the model on the efficacy analysis set.

- **In patients with baseline values ≥ 2.26 mmol/L, a 27% reduction was observed in treated patients vs. 8% in placebo.**
- **Significant increase in HDL-C was observed in BOS-580 treated patients (not shown)**

Dose dependent and numerically higher reductions in HbA1c

Absolute Change in HbA1C



Based on LSmeans with treatment and baseline value effects in the model on the efficacy analysis set.

- **Numerically higher reductions in C-peptide and insulin observed in patients with ≥ 150mg monthly exposure (not shown)**
- **Statistically significant increase in adiponectin levels of up to 77% (placebo adjusted) was observed in BOS-580 treated patients at all dose levels (not shown)**

CONCLUSION

- BOS-580 resulted in a statistically significant reduction in liver fat content as well as markers of liver injury and fibrosis in phenotypic NASH patients with numerically improved markers of metabolic health, including insulin resistance, with monthly subcutaneous doses ≥ 150mg.
- To date, BOS-580 has demonstrated low discontinuation rates in clinical trials. The most commonly observed adverse events have been of GI in nature, which were transient and mild to moderate in severity.
- Further clinical development of BOS-580 for the treatment of NASH is ongoing.

References:
1. Geng L et al. The therapeutic potential of FGF21 in metabolic diseases: from bench to clinic. *Nat Rev Endocrinol* 2020; 16: 654-667.
2. Rader DJ et al. LLF580, an FGF21 analog, reduces triglycerides and hepatic fat in obese adults with modest hypertriglyceridemia. *J Clinical Endocrinology* 2022; 107(1): e57-570.

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