BIO89-100 DEMONSTRATED ROBUST REDUCTIONS IN LIVER MRI-PDFF, FAVORABLE TOLERABILITY AND POTENTIAL FOR EVERY 2 WEEKS DOSING IN A PHASE 1b/2a PLACEBO-CONTROLLED, DOUBLE-BLIND, MULTIPLE ASCENDING DOSE STUDY IN NASH

ROHIT LOOMBA[1], ERIC J. LAWITZ[2], BRIDGETTE BOGGESS FRANEY[3], LINDA MORROW[4], CHAO-YIN CHEN[5], LEO TSENG[5], HANK MANSBACH[5] AND MAYA MARGALIT[5]

[1]NAFLD Research Center, University of California at San Diego, La Jolla, CA, [2]Texas Liver Institute, University of Texas Health San Antonio, San Antonio, TX, [3]Prosciento Clinical Research Unit, Chula Vista, CA, [4]Prosciento, Inc., Chula Vista, CA, [5]89bio, Inc., San Francisco, CA, and Herzliya, Israel; Maya.margalit@89bio.com

INTRODUCTION

- FGF21 is an endogenous hormone that regulates carbohydrate, lipid and energy metabolism. FGF21 analogs improve liver and metabolic abnormalities in non-alcoholic steatohepatitis (NASH).
- BIO89-100 is a long-acting glycoPEGylated FGF21 analog, with promising tolerability and pharmacodynamic effects, and potential for weekly (QW) or every 2 week (Q2W) dosing[1].

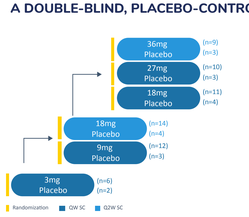
[1]Loomba et al., Abstract #2138, AASLD 2019

OBJECTIVES

To evaluate the effect of administration of multiple, ascending doses of BIO89-100 on safety, tolerability, pharmacokinetics, liver fat as measured by MRI-PDFF and other liver-related and metabolic parameters in subjects with non-alcoholic steatohepatitis (NASH) or with non-alcoholic fatty liver disease (NAFLD) and at high risk of NASH [phenotypic NASH (PNASH)]

METHODS

A DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 1B/2A MAD STUDY (NCT4048135)



KEY INCLUSION CRITERIA

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

*Subjects 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

- 12-week treatment duration + 4-week safety follow up
- 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 (subjects with post-baseline MRI)

RESULTS

Baseline Characteristics

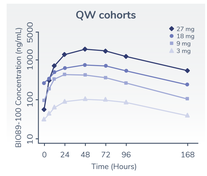
PARAMETER MEAN OR %	PLACEBO (n=19)	POOLED BIO89-100 (n=62)	3MG QW (n=6)	9MG QW (n=12)	18MG QW (n=11)	27MG QW (n=10)	18MG Q2W (n=14)	36MG Q2W (n=9)
Age (years)	52.6	51.7	56.1	49.5	51.5	52.0	51.2	52.5
Male	36.8%	38.7%	16.7%	50%	27.3%	20%	28.6%	88.9%
Weight (kg)	93.6	93.6	87.9	87.2	87.1	94.0	101.5	101.1
BMI (kg/m²)	33.8	34.8	34.3	32.7	32.8	36.8	37.0	34.8
Type 2 Diabetes	63.2%	40.3%	83.3%	33.3%	63.6%	40.0%	21.4%	22.2%
ALT (U/L)	38.8	42.3	45.0	32.8	38.4	53.3	39.1	50.4
AST (U/L)	29.0	31.5	34.5	22.8	30.9	39.0	28.8	38.1
MRI-PDFF (%)	21.8	21.2	22.4	21.4	19.3	22.0	21.6	20.9

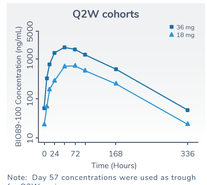
Similar Baseline Characteristics in Subjects with Biopsy-Proven NASH or PNASH

PARAMETER MEAN	NASH (n=15)	PNASH (n=66)	OVERALL (n=81)
Age (years)	50.6	52.2	51.9
Male	20%	42%	38%
Weight (kg)	99.3	92.3	93.6
BMI (kg/m²)	35.4	34.4	34.6
Type 2 Diabetes	26.7%	50%	45.7%
MRI-PDFF (%)	21.2	21.4	21.3
ALT (U/L)	42.9	41.1	41.5
ALT > ULN (45 U/L)	26.7%	36.4%	34.6%
AST (U/L)	34.9	30.0	31.0

Randomized Analysis Set

Steady State Pharmacokinetics – Day 29



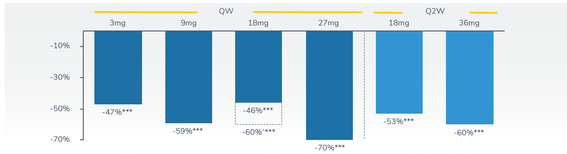


Note: Day 57 concentrations were used as trough for Q2W regimen
Dose proportional PK was observed and exposures were related to total doses regardless of regimen.

RESULTS

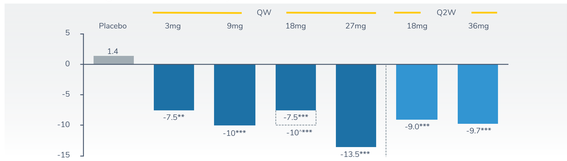
ROBUST REDUCTION IN LIVER FAT IN ALL DOSE GROUPS

Placebo Adjusted Relative Change in Liver Fat at Week 13



MRI Analysis Set; MMRM LS Mean; * p<0.05; ** p<0.01; *** p<0.001 versus placebo; placebo 10% relative increase from baseline
^Excluding two subjects enrolled in BIO89-100 group from sites that were initiated at the end of the study (April 2020)

Absolute Change in Liver Fat (%) from Baseline at Week 13



- 43% of subjects at 27 mg QW normalized liver fat (<5%)
- BIO89-100 significantly reduced liver volume up to 15%

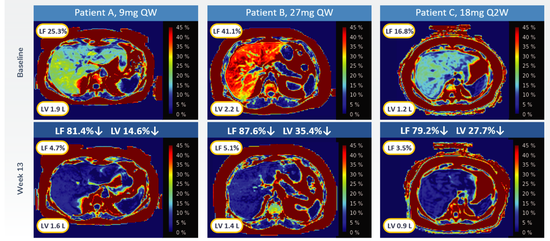
MRI Analysis Set; MMRM LS Mean; * p<0.05; ** p<0.01; *** p<0.001 versus placebo; placebo 10% relative increase from baseline
^Excluding two subjects enrolled in BIO89-100 group from sites that were initiated at the end of the study (April 2020)

Clinically Meaningful Responder Rates at Week 13

	≥30% RESPONSE RATE	≥50% RESPONSE RATE
Placebo	0%	0%
3mg QW	60%**	20%
9mg QW	82%***	54%***
18mg QW	60%**	50%**
27mg QW	86%***	71%***
18mg Q2W	69%**	39%**
36mg Q2W	88%***	50%**

MRI Analysis Set; MMRM LS Mean; * p<0.05; ** p<0.01; *** p<0.001 versus placebo

Substantial Reduction in Liver Fat and Liver Volume Across Doses

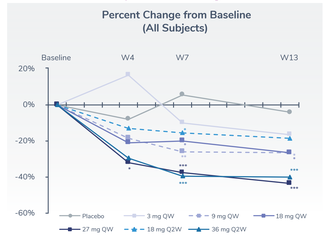


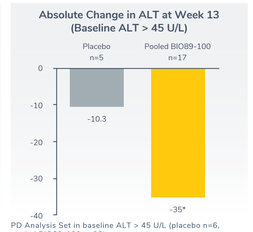
Effects of BIO89-100 were Similar in Biopsy-Confirmed NASH and PNASH BIO89-100 Treated Subjects

- Subjects with biopsy confirmed NASH were randomized to 18mg QW and 18mg Q2W cohorts only.
- The BIO89-100 effect on reducing MRI-PDFF, ALT and Triglycerides are similar in these BIO89-100 treated subjects with NASH and PNASH.

SIGNIFICANT ALT REDUCTION

BIO89-100 Resulted in Clinically Meaningful ALT Reduction with Greater Reduction in Subjects with High ALT

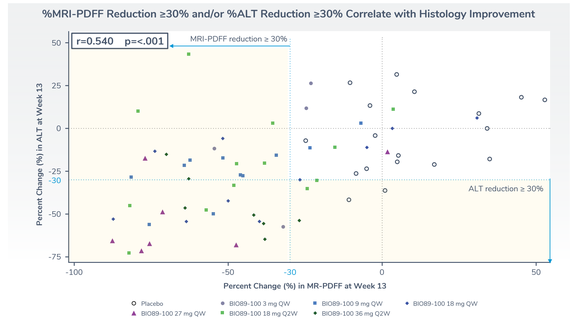




PD Analysis Set in baseline ALT > 45 U/L (placebo n=6, pooled BIO89-100 n=22)

PD Analysis Set; Pre-planned sensitivity analysis; MMRM LS Mean; * p<0.05; ** p<0.01; *** p<0.001 versus placebo

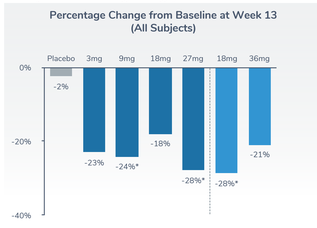
Good Correlation Between Relative Changes in MRI-PDFF and ALT at W13

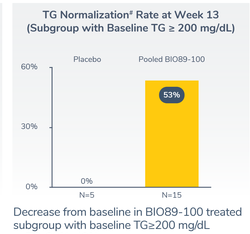


Subjects in both MRI and PD Analysis Set. ALT Pre-planned sensitivity analysis

LIPID AND METABOLIC EFFECTS

BIO89-100 Significantly Reduces Triglycerides with Greater Benefit Observed in Subjects with High Triglycerides

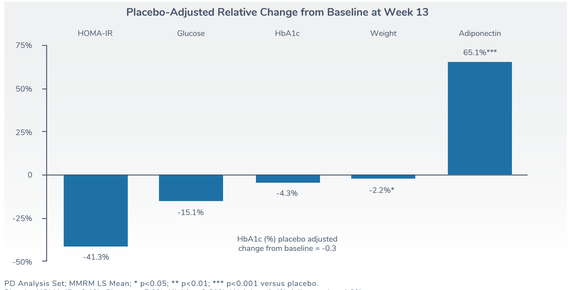




Decrease from baseline in BIO89-100 treated subgroup with baseline TG≥200 mg/dL
- TG: 33%-49%
- Non-HDL: 8%-29%

PD Analysis Set; MMRM LS Mean; * p<0.05; ** p<0.01; *** p<0.001 versus placebo; #TG<150 mg/dL

Improvements in Metabolic Markers with BIO89-100 27mg QW



PD Analysis Set; MMRM LS Mean; * p<0.05; ** p<0.01; *** p<0.001 versus placebo.
Placebo HOMA-IR: -0.1%; Glucose: +7.9%; HbA1c +0.61%; Weight: +1.4% Adiponectin: -4.3%

FAVORABLE SAFETY AND TOLERABILITY

Safety Overview

TREATMENT EMERGENT ADVERSE EVENT (TEAE)	PLACEBO (n=18)	3MG QW (n=7)	9MG QW (n=12)	18MG QW (n=11)	27MG QW (n=10)	18MG Q2W (n=14)	36MG Q2W (n=9)
TEAE Leading to Death	0	0	0	0	0	0	0
TEAE Leading to Discontinuation	0	0	0	0	1[a]	1[b]	0
Serious Adverse Event COVID 19 [Not Drug Related]	0	0	0	0	0	1	1

[a]skin rash; [b]hyperglycemia [Not Drug Related]

Treatment-Related Emergent AEs in ≥ 10% of Pooled BIO89-100 Group

PREFERRED TERM n (%)	PLACEBO (n=18)	POOLED BIO89-100 (n=63)	3MG QW (n=7)	9MG QW (n=12)	18MG QW (n=11)	27MG QW (n=10)	18MG Q2W (n=14)	36MG Q2W (n=9)
Increased Appetite	0.0%	15.9%	4	2	0	2	2	0

- GI related AEs were similar to placebo
  - 9.5% of subjects reported diarrhea in pooled BIO89-100 vs. 11.1% in placebo
  - 4.8% of subjects reported nausea in pooled BIO89-100 vs. 11.1% in placebo
  - 0.0% of subjects reported vomiting in pooled BIO89-100 vs. 0.0% in placebo
- No hypersensitivity AE reported; few mild injection site reaction events reported
- No tremor reported; no adverse effects on blood pressure or heart rate

Safety Analysis Set; one placebo subject received one dose of BIO89-100 3mg and is summarized in 3mg QW group

CONCLUSIONS

- In subjects with NASH, BIO89-100 led to robust, significant and clinically meaningful reductions in liver fat assessed by MRI-PDFF and in ALT, with concurrent beneficial effects on lipids and other metabolic parameters.
- These effects were observed in both QW and Q2W dosing.
- A favorable safety and tolerability profile.
- The promising clinical profile of BIO89-100 supports further development in NASH and severe hypertriglyceridemia (SHTG).