BIO89-100 Demonstrated Robust Reductions in Liver Fat and Liver Fat Volume (LFV) by MRI-PDFF, Favorable Tolerability and Potential for Weekly (QW) or Every 2 Weeks (Q2W) Dosing in a Phase 1b/2a Placebo-Controlled, Double-Blind, Multiple Ascending Dose Study in NASH

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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), and show reductions in triglycerides (TG) that offer promise for treatment of patients with TG ≥500 mg/dL.
- 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]

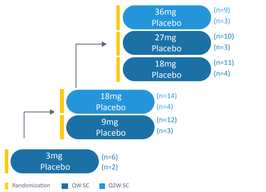
[1]Loomba et al., Abstract #2138, AASLD 2019.

OBJECTIVE

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 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 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/Female	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

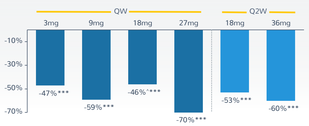
Randomized Analysis Set.

Baseline characteristics were similar between NASH (n=15) and PNASH (n=66) subjects.

RESULTS

ROBUST REDUCTION IN LIVER FAT IN ALL DOSE GROUPS

Placebo Adjusted Relative Change in Liver Fat at Week 13



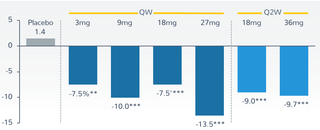
MRI Analysis Set; MMRM LS Mean; * p<0.05; ** p<0.01; *** p<0.001 versus placebo; placebo relative increase of 10% from baseline
†60% relative reduction in liver fat vs. placebo when final 2 patients from this dose group were excluded in a post-hoc analysis. These 2 patients came from 2 separate newly activated sites which came online just before the study closed enrollment in the midst of the COVID pandemic

Clinically Meaningful Responder Rates at Week 13

	PLACEBO	3mg QW	9mg QW	18mg QW	27mg QW	18mg Q2W	36mg Q2W
≥30% Response Rate	0%	60%**	82%***	60%**	86%***	69%**	88%***
≥50% Response Rate	0%	20%	54%***	50%**	71%***	39%**	50%**

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

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

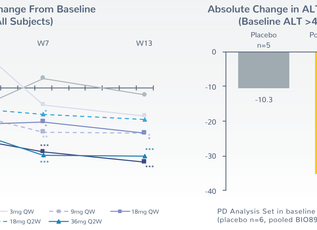


- 43% of subjects at 27mg QW normalized liver fat (<5%).

MRI Analysis Set; MMRM LS Mean; * p<0.05; ** p<0.01; *** p<0.001 versus placebo
†10% absolute reduction in liver fat from baseline when final 2 patients from this dose group were excluded in a post-hoc analysis. These 2 patients came from 2 separate newly activated sites which came online just before the study closed enrollment in the midst of the COVID pandemic

SIGNIFICANT ALT REDUCTION

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

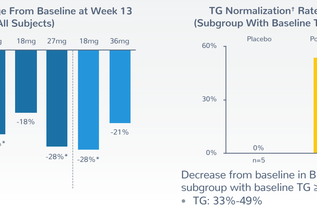


PD Analysis Set; Pre-planned sensitivity analysis; MMRM LS Mean; *p<0.05; **p<0.01; ***p<0.001 versus placebo.

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

LIPID EFFECTS

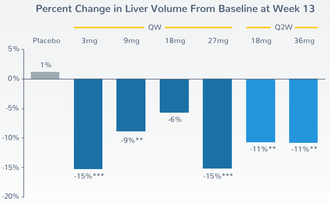
BIO89-100 Significantly Reduces Triglycerides With Greater Benefit Observed in Subjects With High Triglycerides



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

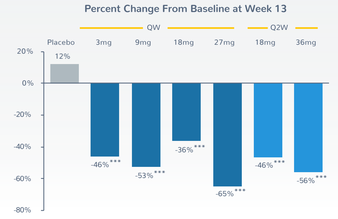
PD Analysis Set; MMRM LS Mean; *p<0.05; **p<0.01; ***p<0.001 versus placebo; †TG<150 mg/dL.

BIO89-100 Significantly Reduces Liver Volume



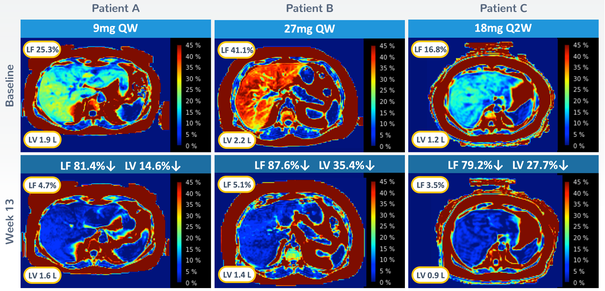
MRI Analysis Set; MMRM LS Mean; *p<0.05; **p<0.01; ***p<0.001 versus placebo.

BIO89-100 Significantly Reduces Liver Fat Volume (LFV)

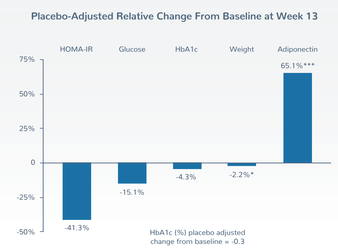


MRI Analysis Set; MMRM LS Mean adjusting for baseline, treatment, visit and treatment x visit; *p<0.05; **p<0.01; ***p<0.001 versus placebo.

Examples of Substantial Reductions in Liver Fat and Liver Volume by MRI-PDFF From Individual Subjects



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

- There were 2 discontinuations due to adverse events (1 skin rash and 1 event of hyperglycemia that was not considered treatment related); and 2 serious adverse events, both Covid-19 infections that were not considered treatment related.
- No hypersensitivity AE reported with a few mild ISRs reported.
- No adverse effects on blood pressure or heart rate.

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

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

- 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

CONCLUSIONS

- In subjects with NASH, BIO89-100 led to robust, significant, and clinically meaningful reductions in liver fat and liver fat volume 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).