BIO89-100, a Novel Glycopegylated FGF21 Analogue, Demonstrates Robust Reduction in Serum Lipids and Long Half-life in a Phase 1 Randomized, Controlled Single Ascending Dose Trial in Healthy Subjects

ROHIT LOOMBA[1], HANK MANSBACH[2], LEO TSENG[2], CHAO-YIN CHEN[2], MOTI ROSENSTOCK[2], GEORGE ATIEE[3] and MAYA MARGALIT[2]

[1]NAFLD Research Center, University of California San Diego, San Diego, CA, USA, [2]Clinical Development, 89bio Ltd., Herzliya, Israel and San Francisco, CA, USA, [3]Worldwide Clinical Trials, San Antonio, TX, USA

INTRODUCTION

- FGF21 is a non-mitogenic metabolic hormone that affects energy expenditure and glucose and lipid metabolism. FGF21 analogues in development have been shown to improve metabolic and liver-related abnormalities related to nonalcoholic steatohepatitis (NASH) in pre-clinical models and human subjects, including NASH patients.
- BIO89-100 is a novel, long-acting glycoPEGylated recombinant human FGF21, with promising effects on metabolic and liver-related parameters in mice and monkeys.

OBJECTIVES

The objectives of this study were to evaluate the effect of administration of single, ascending, subcutaneous (SC) doses of BIO89-100 on safety, tolerability and pharmacokinetic profile, immunogenicity, and pharmacodynamic endpoints in healthy subjects.

METHODS

Double-blind, randomized, single ascending dose (SAD) study in 58 healthy subjects. Subjects received a single SC dose of BIO89-100 at 0.45 mg, 1.2 mg, 3 mg, 9.1 mg, 18.2 mg, 39 mg, or 78 mg, or placebo in a 6:2 ratio (7:3 ratio for the 9.1 mg dose) and were followed for 4 weeks.

RESULTS

- Similar baseline characteristics in pooled BIO89-100 and placebo groups.
- Mean baseline labs are within normal range.

MEAN (SD) OR %	POOLED BIO89-100 (n=43)	PLACEBO (n=15)
Age (years)	39.3 (10.0)	39.4 (9.3)
Male (%)	86%	87%
White (%)	67%	53%
Hispanic/Latino (%)	44%	40%
Weight (kg)	79.9 (11.1)	83.0 (14.9)
BMI (kg/m^2)	26.5 (3.1)	27.3 (3.0)
Triglycerides (mg/dL)	92.1 (33.9)	99.3 (42.0)
Total Cholesterol (mg/dL)	182.2 (28.8)	197.5 (31.8)
HDL (mg/dL)	46.6 (9.2)	50.8 (12.3)
LDL (mg/dL)	122.2 (26.9)	129.6 (26.6)
Glucose (mg/dL)	87.8 (7.3)	89.3 (6.1)
Insulin (uIU/mL)	7.3 (3.1)	7.3 (2.9)
ALT (U/L)	21.0 (7.9)	22.3 (5.7)
AST (U/L)	20.3 (4.5)	19.5 (4.0)
GGT (U/L)	25.2 (10.7)	25.4 (8.7)

RESULTS

BIO89-100 WAS GENERALLY SAFE AND WELL TOLERATED ACROSS ALL STUDIED DOSES

No deaths, serious adverse events (SAEs), or discontinuations due to adverse events.

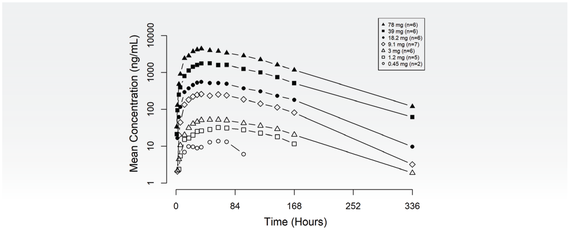
- The most commonly reported treatment-related AEs in at least 2 subjects in the pooled BIO89-100 group were injection-site reactions and headache, all of which were reported as mild.
- Injection-site reactions were more frequent in the 39 mg cohort, likely due to a larger injection volume per injection in that cohort.
- No clinically meaningful trends were observed in gastrointestinal events, laboratories, ECGs or vital signs, including blood pressure or heart rate changes. No tremors were reported.
- Five of 43 BIO89-100–treated subjects tested positive for anti-drug antibodies (ADAs); however, all titers were low (≤16) and did not appear to affect the PK or safety profile.

Treatment-Related TEAEs Reported in ≥ 2 Subjects in Pooled BIO89-100 Treatment Group

	PLACEBO	BIO89-100							POOLED
PREFERRED TERM		0.45 MG	1.2 MG	3 MG	9.1 MG	18.2 MG	39 MG	78 MG	BIO89-100
n (%)	(N=15)	(N=6)	(N=6)	(N=6)	(N=7)	(N=6)	(N=6)	(N=6)	(N=43)
ANY	3 (20.0)	0	0	0	1	3	6	3	13 (30.2)
INJECTION-SITE INDURATION	1 (6.7)	0	0	0	1	0	5	1	7 (16.3)
INJECTION-SITE ERYTHEMA	1 (6.7)	0	0	0	0	0	3	2	5 (11.6)
INJECTION-SITE PAIN	0	0	0	0	0	0	2	0	2 (4.7)
HEADACHE	1 (6.7)	0	0	0	0	2	0	0	2 (4.7)

BIO89-100 HAD A GENERALLY DOSE-PROPORTIONAL PK PROFILE

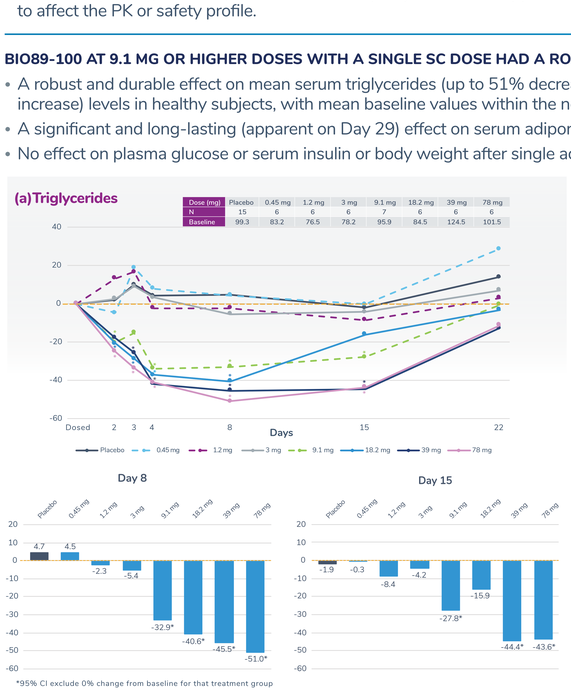
Mean Serum Concentration-Time Data of BIO89-100 After Single SC Injections: Average Elimination Half-life Was ~55-100 Hours



BIO89-100 AT 9.1 MG OR HIGHER DOSES WITH A SINGLE SC DOSE HAD A ROBUST, DURABLE EFFECT ON SERUM LIPIDS & ADIPONECTIN

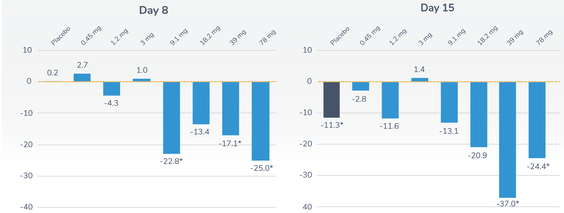
- A robust and durable effect on mean serum triglycerides (up to 51% decrease), LDL-cholesterol (up to 37% decrease), and HDL-cholesterol (up to 36% increase) levels in healthy subjects, with mean baseline values within the normal range [Figures a-c, mean % changes from baseline for all parameters].
- A significant and long-lasting (apparent on Day 29) effect on serum adiponectin (up to +146% increase) [Figure d, mean % change from baseline].
- No effect on plasma glucose or serum insulin or body weight after single administrations of BIO89-100 to healthy subjects.

(a) Triglycerides

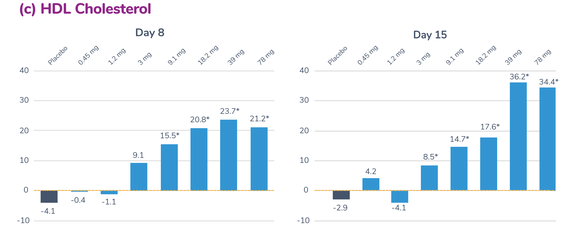


*95% CI exclude 0% change from baseline for that treatment group

(b) LDL Cholesterol



(c) HDL Cholesterol

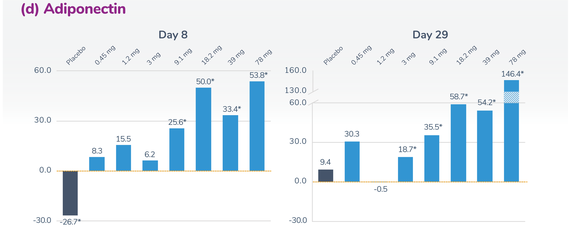


Effect on Lipids of BIO89-100 (Placebo-Adjusted)

% CHANGE FROM BL	BIO89-100				
LS MEAN DIFF. *	<9.1 MG	9.1 MG	18.2 MG	39 MG	78 MG
Triglyceride Day 8	-8.7	-38.8	-47.5	-46.3	-55.3
P-value	0.43	0.01	<0.01	<0.01	<0.0001
Triglyceride Day 15	-4.7	-26.4	-16.3	-38.7	-41.4
P-value	0.67	0.07	0.30	0.01	<0.01
LDL Day 8	-2.2	-23.4	-14.4	-16.2	-25.1
P-value	0.62	<0.0001	0.02	<0.01	<0.0001
LDL Day 15	5.9	-2.9	-10.4	-24.6	-13.0
P-value	0.18	0.61	0.09	<0.0001	0.03
HDL Day 8	5.7	20.2	23.1	25.9	23.0
P-value	0.11	<0.0001	<0.0001	<0.0001	<0.0001
HDL Day 15	5.2	17.6	18.8	37.2	35.0
P-value	0.15	<0.0001	<0.0001	<0.0001	<0.0001

*Post-hoc analyses using mixed-effect model repeat measurement with percentage change from baseline as the response variable, fixed effects for treatment, visit and the interaction between treatment, and visit and the observed value at baseline as a covariate. Least square (LS) mean difference are BIO89-100 group minus placebo.

(d) Adiponectin



CONCLUSIONS

- At single doses up to 78 mg, BIO89-100 was generally safe and well tolerated in healthy subjects, with a generally dose-proportional PK profile. Supportive of weekly or once-every-2-weeks dosing regimens.
- In healthy subjects, single doses of BIO89-100 led to robust and durable reductions in serum triglycerides and LDL cholesterol and increases in HDL cholesterol and adiponectin.
- In an ongoing study (BIO89-100-002), BIO89-100 is being administered weekly or every-other-week to patients with NASH or non-alcoholic fatty liver disease (NAFLD) with high risk of NASH, to evaluate effect on liver fat content (by MRI-PDFF) and other liver-related and metabolic parameters.