BIO89-100, a novel glycoPEGylated FGF21 analogue, is efficacious following weekly and every 2-week subcutaneous dosing in diabetic cynomolgus monkeys

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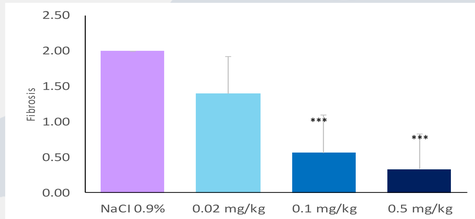
INTRODUCTION

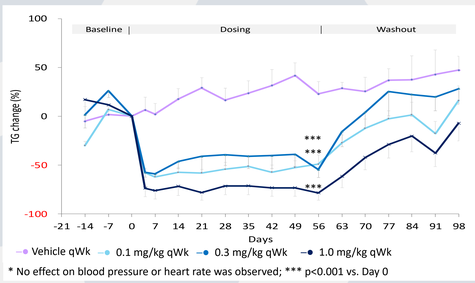
BIO89-100, a novel site-specific glycoPEGylated analogue of fibroblast growth factor 21 (FGF21), is being developed for the treatment of nonalcoholic steatohepatitis (NASH). FGF21, an endogenous metabolic hormone, is a key regulator of carbohydrate and lipid metabolism, with potential anti-fibrotic effects. BIO89-100 was designed using site-specific mutations and glycoPEGylation to delay degradation and decrease dosing frequency. It was shown to improve liver-related and metabolic parameters in 2 mouse models of NASH [Stelic Animal Model (STAM) and diet-induced NASH (DIN) model; Figure 1] and in spontaneously diabetic cynomolgus monkeys using a subcutaneous (sc), once a week (qWk) dosing regimen for 8 weeks (Figure 2)].

Figure 1. Effect of BIO89-100 on fibrosis – mouse DIN model



*** p<0.001 vs. vehicle
BIO89-100 and vehicle administered sc every 3 days
Obeticholic acid, 25 mg/kg, tested as positive control showed minimal effect.

Figure 2. Effect on Triglycerides: Mean change from baseline (%) - spontaneously diabetic cynomolgus monkeys



* No effect on blood pressure or heart rate was observed; *** p<0.001 vs. Day 0

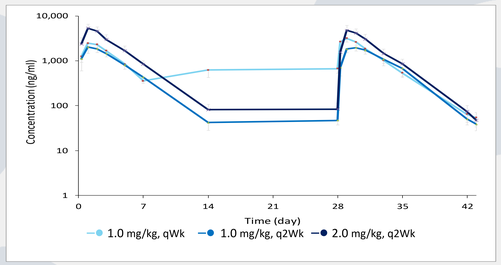
AIM

The objective of the study was to assess the pharmacodynamic effects and pharmacokinetics of BIO89-100 following sc dosing qWk (1 mg/kg) or every 2 weeks (q2Wk; 1 or 2 mg/kg) in spontaneously diabetic cynomolgus monkeys.

RESULTS

The half-life of BIO89-100 was approximately 50 hours. The exposure profile of the qWk and q2Wk regimens was similar, except for higher trough levels on Day 14 and Day 28 with the qWk dose (Figure 3). Exposure to BIO89-100 (AUC and Cmax) increased in a proportional manner for the 1 and 2 mg/kg q2Wk dose levels.

Figure 3. BIO89-100 area under the concentration-time curve following once or every two weeks



Statistically significant reductions were observed in body weight (Figure 4), food intake, glucose, LDL (Figure 5), TG (Figure 6), HbA1c (Figure 7) along with improvement in oral glucose test results (Figure 8) and an increase in adiponectin levels (Figure 9) in all BIO89-100-treated groups vs. the vehicle group. Change in median ALT levels from baseline to Day 28 was between -15.4% to - 42.7% in the BIO89-100 treated groups vs.+8.9% in the vehicle group. BIO89-100 was generally well tolerated, with no GI-related adverse effects or other safety findings.

METHODS

- **ANIMAL MODEL**
  - Spontaneously diabetic cynomolgus monkeys
  - Baseline measures (means): age: 17.2 years; weight: 8.4 kg; HbA1c: 9.7%; TG: 305 mg/dL; ALT: 89.8 U/L
- **STUDY DESIGN**
  - 4 groups (6 animals per group): 0, 1.0 mg/kg qWk, 1.0 mg/kg q2Wk, 2.0 mg/kg q2Wk (sc dosing)
  - 2 weeks baseline; 4 weeks treatment period; 2 week washout
- **PARAMETERS MEASURED**
  - Body weight, food intake, glycemic parameters, serum lipids, adiponectin, ALT
  - Pharmacokinetics

Figure 4. Body Weight: Mean change from baseline (%)

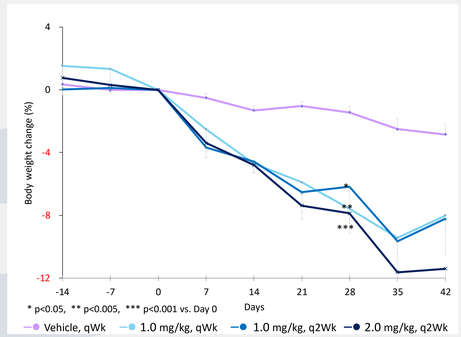


Figure 5. LDL: Mean change from baseline (%)

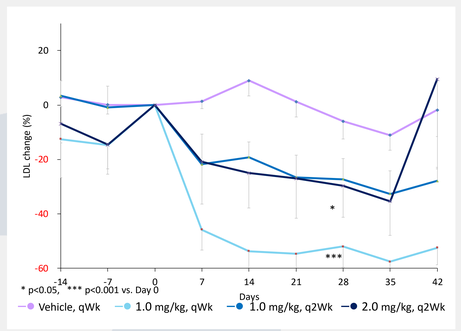


Figure 6. Triglycerides: Mean change from baseline (%)

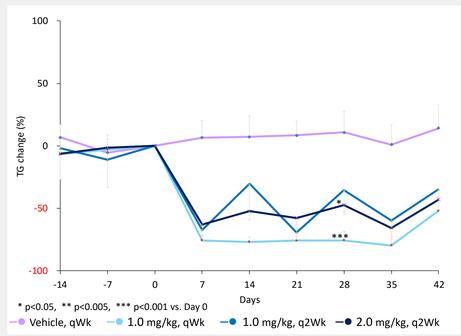


Figure 7. HbA1c: Mean change from baseline (%)

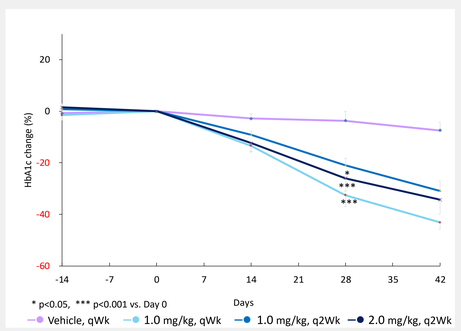


Figure 8. Oral glucose tolerance test: Mean glucose area under the concentration-time curves (AUCs)

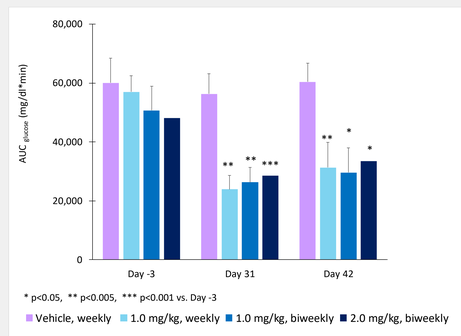
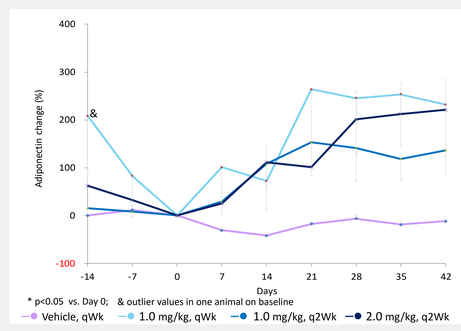


Figure 9. Adiponectin: Mean change from baseline (%)



CONCLUSIONS

- **In this study in spontaneously diabetic cynomolgus monkeys, BIO89-100 demonstrated:**
  - ✓ **Statistically significant PD effects on body weight, key metabolic parameters and ALT levels**
  - ✓ **PK and PD profiles suggesting a potential for once a week or once every two weeks dosing in humans**
  - ✓ **A generally comparable effect on PD parameters between the active dosing groups**
- **These findings suggest potential utility of BIO89-100 for treatment of patients with NASH**
- **A single ascending dose clinical study in healthy volunteers is ongoing**

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