2413-C

Population Pharmacokinetic/Pharmacodynamic Modeling of Hepatic Fat Fraction, PRO-C3, and ALT Suggests Equivalent Efficacy Between Once-monthly and Bi-weekly Dosing BOS-580 in Phenotypic NASH Patients

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INTRODUCTION

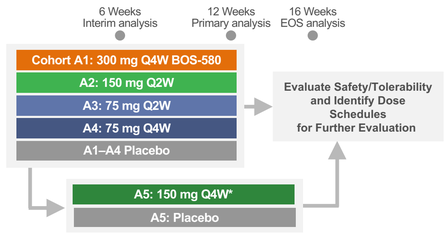
- Fibroblast growth factor 21 (FGF-21) has important roles in regulating energy balance, and glucose and lipid metabolism.[1]
- FGF21 analogs may increase non-alcoholic steatohepatitis (NASH) resolution and improve fibrosis in NASH patients.[1]
- BOS-580 is an investigational FGF21-IgG fusion protein highly engineered to have an extended serum half-life of 21 days in humans after subcutaneous administration, suggesting the feasibility of once-monthly dosing.[2]
- In a Phase 2a, Part A study, 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 improvements in the markers of metabolic health, including insulin resistance.[3]

AIMS

- Evaluate population pharmacokinetics (Pop-PK) of BOS-580 in subjects with phenotypic NASH in Phase 2a Part A study (BOS-580-201) following repeated dosing over 12 weeks.
- Assess the effects of BOS-580 doses and dosing regimens on pharmacodynamic (PD) biomarkers, hepatic fat fraction (HFF), PRO-C3, or ALT.

STUDY DESIGN AND METHODS

Phase 2a, Part A (BOS-580-201): A randomized, double-blind, placebo-controlled trial in patients with phenotypic NASH



Planned Randomization
n=75, 4:1

Key Inclusion Criteria
- BMI 30–45 kg/m^2
- 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)

*6 of 15 subjects received 30 mg BOS-580 as first dose followed by 150 mg Q4W (Q4W, once-monthly; Q2W, bi-weekly)
Total randomized = 102

Strategy/Methods for PK/PD Modeling

- Generate Pop-PK estimates from previous Phase 1 single-administration and repeat-administration studies with rich PK data set.[2,4]
- Perform Bayesian analysis on Phase 2a Part A PK data to generate individual PK profiles using the prior Pop-PK estimates.
- Estimate all PK population characteristics from Phase 2a Part A study with only the covariate-based power terms associated with both clearance and volume versus weight.
- Perform a sequential PK/PD analysis on HFF data using individual predicted PK profiles from the Bayesian analysis. Similar analysis was done for PRO-C3 and ALT. Assess goodness of fit for the HFF, PRO-C3, and ALT PK/PD analysis.
- For PRO-C3, the effect of % PRO-C3 reduction for whole cohort and for subjects with baseline >13 ng/mL were evaluated.
- For ALT, baseline ALT >48 IU (male) and >33 IU (female) were also examined.[5] Four parameters were evaluated:
  - Absolute reduction of 17 IU
  - Probability of number of patients achieving 30% and 50% reduction in ALT
  - Median % ALT reduction
  - Effect of baseline ALT on % reduction

PK/PD Model Structure: Indirect Response Model With Inhibition of HFF, PRO-C3, and ALT Production

$$\frac{dE}{dt} = Kin * \left(1 - \frac{Emax * C}{C + EC50}\right) - Kout * E$$

E: HFF, PRO-C3, or ALT
Kin: Natural production rate of HFF, PRO-C3, or ALT
C: Predicted PK concentration
Kout: First-order elimination rate of HFF, PRO-C3, or ALT
*EC*50: Potency
Emax: Maximum effect

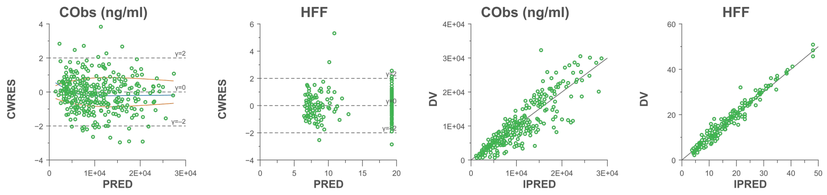
RESULTS

Population Pharmacokinetics (Pop-PK) Analysis and Pharmacokinetics/Pharmacodynamic (PK/PD) Model

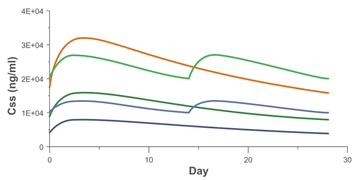
- Pop-PK Base Model
  - The optimal PK model was identified to be a one-compartment model with first-order absorption and elimination
- Pop-PK Covariate Model
  - A full covariate search was performed with sex, ethnicity, race, height, weight, and BMI effects on all PK parameters tested
  - Only weight was correlated to both volume and clearance and therefore it was used to optimize the PK model
- A Population PK/PD model was developed for PD biomarkers, HFF, PRO-C3, or ALT. The Population PK/PD model was used to run simulations to predict the percent (%) reduction of the biomarkers at different doses and dosing regimens.
- Goodness of fit was assessed for the PK data and all 3 biomarkers
  - CWRES (conditional weighted residuals) vs PRED (average predicted)
  - DV (observed) vs IPRED (individual predicted) concentration
  - DV (observed) vs IPRED (individual predicted) concentration
  - Individual predictions
  - Visual predictive checks

Conditional weighted residues (CWRES) and dependent variables (DV) vs individual predicted parameters indicate a robust Pop-PK/PD model

- Most of the CWRES data points are within −2 and 2 with no bias
- The DV vs IPRED data are symmetrically distributed along the x=y axis, indicating no obvious bias in the Pop-PK and PK/PD model for all 3 biomarkers: HFF, PRO-C3, ALT (PRO-C3 and ALT data not shown)

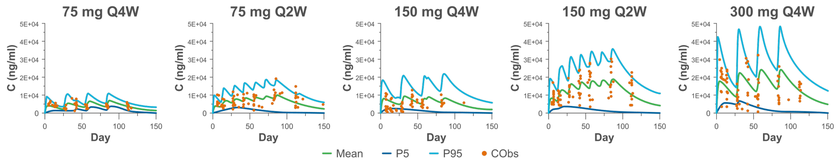


Pop-PK data show dose-proportional increase in exposure of BOS-580 at steady-state in Phase 2a Part A

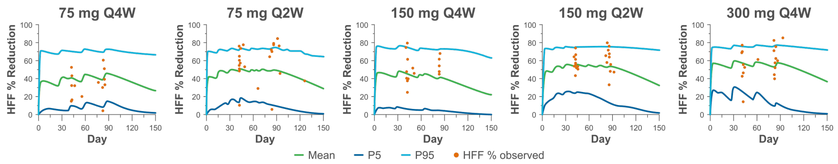


Dose	C_{trough} µg/mL	AUC_{tau} d*µg/mL
75 mg Q4W	3.92	167
75 mg Q2W	9.92	167
150 mg Q4W	7.88	334
150 mg Q2W	19.8	334
300 mg Q4W	15.7	667

Pop-PK model predicted vs observed BOS-580 concentrations by dose and dosing regimen: most data points are within 90% confidence interval

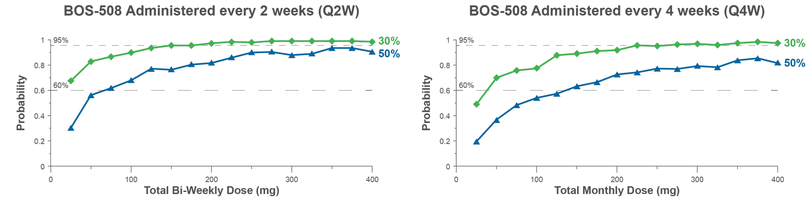


Model predicted vs observed % HFF reduction by dose and dosing regimen: most data points are within 90% confidence interval



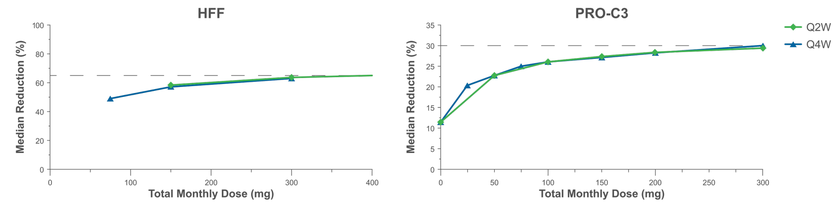
Probability of ≥30% or ≥50% reduction in HFF vs dose

- With ≥150 mg total monthly dose: a) >60% patients are predicted to reduce ≥50% HFF relative to baseline and b) ~95% patients to reduce HFF by ≥30%
- Similar outcome for Q2W or Q4W administration for the same total monthly dose

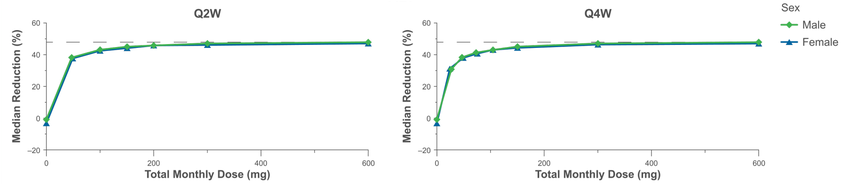


Once-monthly and bi-weekly dosing regimens resulted in similar median % HFF and PRO-C3 (baseline >13 ng/mL) reduction at Week 12 for the same total monthly dose

- Median reduction of ~65% HFF and ~30% PRO-C3 is predicted at the 300 mg once-monthly dose of BOS-580



Once-monthly and bi-weekly dosing regimens resulted in similar median % ALT reduction at Week 12 for the same total monthly dose



ALT PK/PD analysis stratified by sex due to baseline differences between males and females; there is no sex effect on reduction of ALT

SUMMARY

- Pop-PK analysis indicated a dose-proportional increase in BOS-580 AUC at steady-state.
- Evaluation of several goodness of fit parameters indicated that the observed and predicted residuals and variables highly correlated with no obvious bias and the Pop-PK and PK/PD models captured the PK data and 3 PD parameters with 90% confidence interval.
- At doses ≥150 mg monthly, >60% of patients are expected to reduce HFF by ≥50%.
- Q4W is equally effective as Q2W in lowering HFF, PRO-C3, and ALT, and these reductions are independent of the dosing regimen for the same total monthly dose.
- Pop-PK PD modeling of long-acting BOS-580 with phenotypic NASH patients demonstrated that once-monthly and bi-weekly dosing resulted in similar effect on efficacy biomarkers.

CONCLUSION

- Pop PK/PD modeling of BOS-580 once-monthly dosing predicts similar results as bi-weekly dosing for the reduction in HFF, PRO-C3, and ALT in patients with phenotypic NASH, supporting the development of long-acting BOS-580 as a once-monthly FGF21 analog for the treatment of NASH.

DISCLOSURES

Swapan K Chowdhury, MD, Tatjana Odrljin, MD, Alicia Clawson, Etienne Dumont, MD, and **Eric Svensson, MD,** are employees of Boston Pharmaceuticals and may hold stock. **Aruna Dontabakhtuni** is an employee of Pharmapro Consulting Inc, a consultant for Boston Pharmaceuticals. **Vijay Bhargava** is an employee of Nejay Consultants, Inc, a consultant for Boston Pharmaceuticals. **Serge Guzy** is an employee of Poppharm Pharmacoemetric Services, a consultant for Boston Pharmaceuticals.

REFERENCES

1. Tillman EJ et al. FGF21: an emerging therapeutic target for non-alcoholic steatohepatitis and related metabolic diseases. *Front Endocrinol* 2020;14(11):601290. **2.** Rader DJ et al. LLF580, an FGF21 analog, reduces triglycerides and hepatic fat in obese adults with modest hypertriglyceridemia. *J Clin Endocrinol* 2022;107(1):e57-570. **3.** Loomba, R et al. 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. 2023 EASL Congress, Vienna, Austria 21-24 June. **4.** Data on file. **5.** Valenti L, et al. Definition of healthy ranges for alanine aminotransferase levels: a 2021 update. *Hepatol Commun* 2021;5(11):1824-1832.