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Low Immunogenicity Rates in Phenotypic MASH Patients Treated for 12 Weeks With Once-monthly and Bi-weekly Subcutaneous Dosing of BOS-580

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INTRODUCTION

Anti-drug antibodies (ADAs) are a clinical measure of protein therapeutic immunogenicity. Immune response to protein therapeutics can alter or reduce their efficacy and may be associated with adverse effects. BOS-580 is an investigational, highly engineered dimer of human FGF21-IgG fusion protein designed to have reduced immunogenicity due to expression in a mammalian cell line and proper glycosylation. Furthermore, BOS-580 has a unique disulfide bond and distinct point mutations that leads to extended protein stability and circulating half-life.[1,2]

In a Phase 1 study, BOS-580 showed a dose-proportional increase in exposure with a half-life of about 21 days, suggesting the feasibility of once-monthly or bi-weekly dosing. In a Phase 2a study, BOS-580 resulted in a statistically significant reduction in liver fat content as well as markers of liver injury and fibrosis in phenotypic metabolic dysfunction-associated steatohepatitis (MASH; formerly known as NASH) patients with improvements in markers of metabolic health, including insulin resistance.[3] Here, we report the immunogenicity of BOS-580 in a randomized, double-blind, placebo-controlled Phase 2a, Part A study.

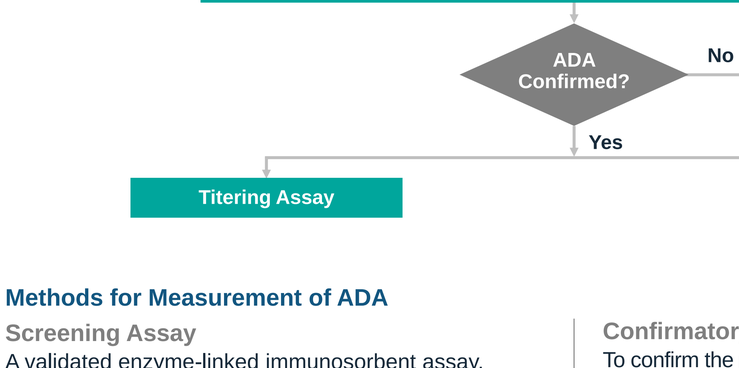
OBJECTIVES

- Develop and validate a bioanalytical method to determine the presence of anti–BOS-580 and anti–FGF21 antibodies in human serum.
- Evaluate ADA formation following subcutaneous once-monthly or bi-weekly administration of BOS-580 for 12 weeks in patients with phenotypic MASH in the Phase 2a, Part A study.
- Assess the effects of BOS-580 doses and dosing regimens on ADA formation.

METHODS

STUDY DESIGN

Phase 2a, Part A: A randomized, double-blind, placebo-controlled trial of BOS-580 in patients with phenotypic MASH[3]



Randomized
N=102

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)

[a]6 of 15 subjects received BOS-580 30 mg as first dose followed by BOS-580 150 mg Q4W.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LSM, liver stiffness measure; MRI-PDFF, magnetic resonance imaging proton density fat fraction; PRO-C3, N-terminal type III collagen propeptide; Q2W, once every 2 weeks; Q4W, once every 4 weeks; VCTE, vibration controlled transient elastography.

Overview of ADA Analysis for BOS-580

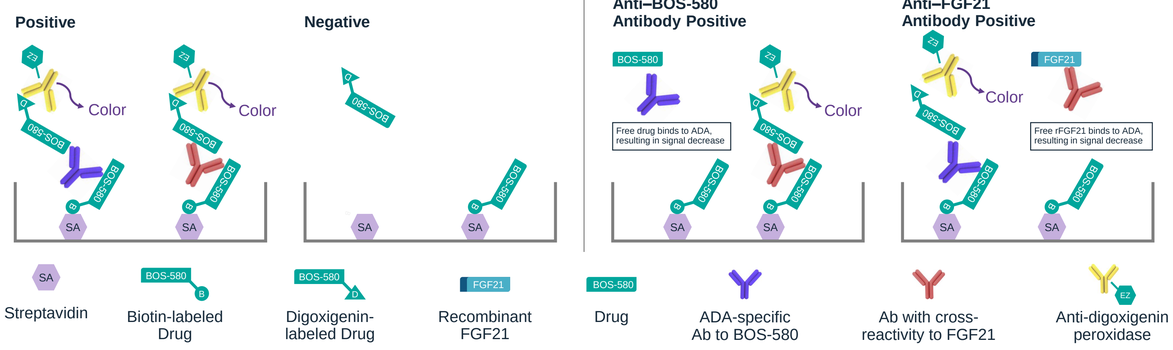
Methods for Measurement of ADA

Screening Assay

A validated enzyme-linked immunosorbent assay, which is shown in the figure below, is used to screen for the presence of anti–BOS-580 and anti–FGF21 antibodies in human serum. The ADAs present in serum bind to biotin- and digoxigenin-labeled drug and is detected with anti–digoxigenin peroxidase antibody

Confirmatory Assay

To confirm the presence of ADAs in potentially positive samples, a competitive assay is applied. As shown in the figure below, excess BOS-580 or recombinant human FGF21 is added to samples. The binding of ADAs with the capture/detection is prevented by free drug or FGF21. This results in a decrease in assay signal and the extent of decline is quantitated as percent inhibition.



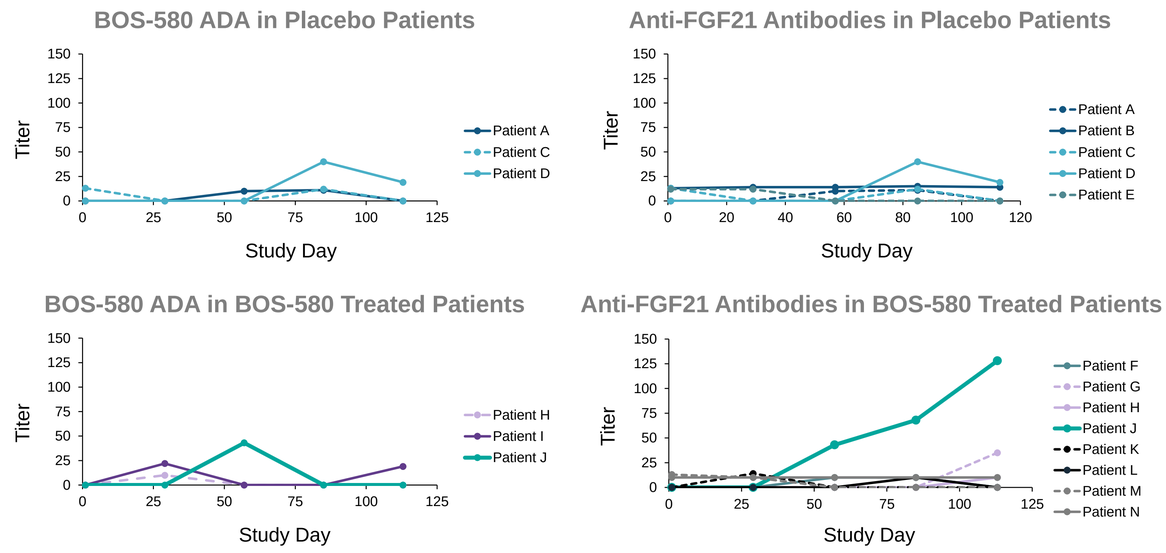
RESULTS

ADA Data Summary for BOS-580 from Phase 2a, Part A Study

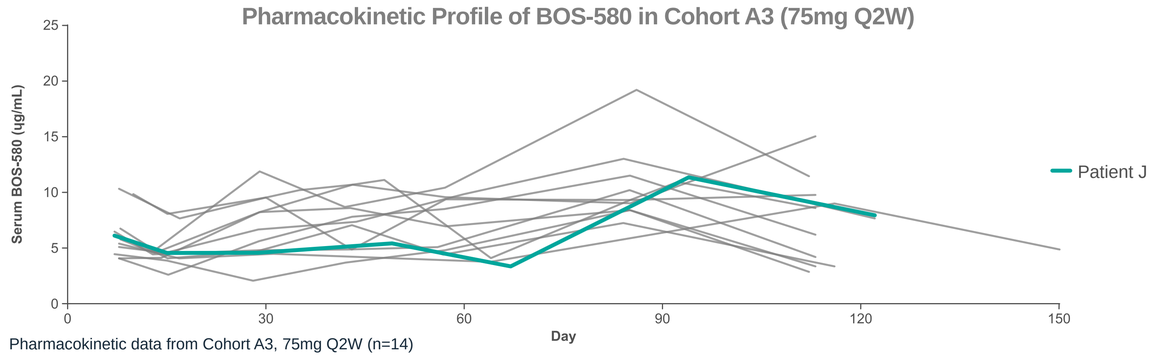
		Total Confirmed ADA Positives		BOS-580 ADA		Anti–FGF-21 Antibodies	
No. of Patients		No. of Patients	% of Patients	No. of Patients	% of Patients	No. of Patients	% of Patients
Placebo	37	5	13.5	3	8.1	5	13.5
BOS-580 Treated	65	9	13.9	3	4.6	8	12.3

At baseline, anti-FGF21 antibodies were detected in five patients (placebo, n=3; BOS-580 treated, n=2).

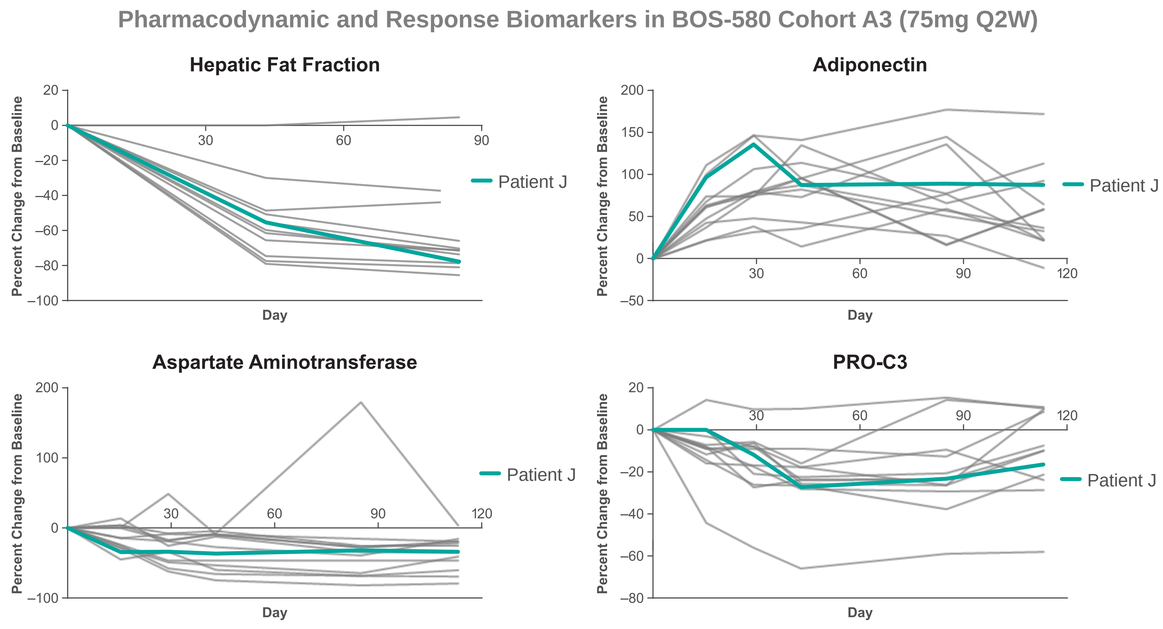
Schematic Presentation of All ADA Data



Treatment-emergent anti-FGF21 antibodies were detected in one (Patient J) out of 65 patients exposed to BOS-580 and it was determined to have no effect on their pharmacokinetic or pharmacodynamic parameters.



Pharmacokinetic data from Cohort A3, 75mg Q2W (n=14)



Pharmacodynamic and response data from Cohort A3, 75mg Q2W (n=14).

RESULTS AND DISCUSSION

- BOS-580 showed low and transient ADA responses detected at only one or two measurements. Anti–BOS-580 and anti–FGF21 antibody titers were low.
- At baseline, anti–FGF21 antibodies were detected in five patients (placebo, n=3; BOS-580 treated, n=2).
- Treatment-emergent anti-FGF21 antibodies were detected in one patient (Pt J) out of 65 patients exposed to BOS-580. Consecutive and increasing titers had no impact on pharmacokinetic and pharmacodynamic response, and there were no adverse events reported.
- These data are consistent with previously reported Phase 1 data.[4]

CONCLUSION

BOS-580 was designed to have reduced immunogenicity due to expression in a mammalian cell line and proper glycosylation. The data show that most ADAs were transient and detected at only 1 or 2 measurements with low titers. One of 65 (1.5%) BOS-580-treated patients presented with treatment-emergent anti-FGF21 antibodies that had no impact on clinical symptoms, pharmacokinetic, or pharmacodynamic parameters.

REFERENCES

1. Flintegaard TV et al. *Endocrinology*. 2010;151(11):5326-5336. **2.** Zhou Q, Qiu H. *J Pharm Sci*. 2019;108(4):1366-1377. **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. EASL Congress 2023; June 21-24, 2023; Vienna, Austria. 4. Rader DJ et al. *J Clin Endocrinol Metab*. 2022;107(1):e57-e70.

DISCLOSURES

SKC, AM, AC, MW, TO, GB, and ES: employees and/or shareholders of Boston Pharmaceuticals.