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 FGF21-15r 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 steatohepatosis (MASH) formerly known as NASH in 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 biosimilarity 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 MASH3

- 6 Week Intake Analysis
- 12 Week Primary Analysis
- 10 Week BOS-580 Analysis

- Randomized
- No.102

Key Inclusion Criteria
- BMI 25–35 kg/m²
- Lower fat MRI–FGF21 ≥10%
- ALT >45 U/L
- LSM 7.0–9.9 kPa

Key Exclusion Criteria
- Any previous immunoglobulin treatment
- Malignancy
- Active infection
- HIV
- Hepatitis
- Renal failure

Schematic Presentation of All ADA Data

Overview of ADA Analysis for BOS-580

Develop and Validate Sensitive Screening and Confirmatory ADA Assays

Methods for Measurement of ADA

Screening Assay

A validated enzyme-linked immunosorbent assay (ELISA) 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

DATA A SUMMARY FOR BOS-580 FROM PHASE 2A, PART A STUDY

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>No. of Patients</th>
<th>% of Patients</th>
<th>No. of Patients</th>
<th>% of Patients</th>
<th>No. of Patients</th>
<th>% of Patients</th>
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</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>37</td>
<td>13.5</td>
<td>3</td>
<td>8.1</td>
<td>5</td>
<td>13.5</td>
</tr>
<tr>
<td>BOS-580 Treated</td>
<td>65</td>
<td>13.9</td>
<td>3</td>
<td>4.6</td>
<td>8</td>
<td>12.3</td>
</tr>
</tbody>
</table>

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

Schematic Presentation of All ADA Data

Pharmacokinetic Profile of BOS-580 in Cohort A3 (75mg Q2W)

Pharmacodynamic and Response Biomarkers in BOS-580 Cohort A3 (75mg Q2W)

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


DISCLOSURES

MSK, B, EC, W, TO, and DB: employees and/or shareholders of Boston Pharmaceuticals.