WED-220

BOS-580, a long-acting FGF21 analogue, treatment shows beneficial changes in the circulating lipidome and improves MASEF score in patients with phenotypic metabolic dysfunction-associated steatohepatitis in a Phase 2a randomized, placebo-controlled, 12-week study

Gerard Bain, Alicia Clawson, Juan Carlos Lopez-Talavera, Tatjana Odrljin

Boston Pharmaceuticals, Cambridge, MA, United States

BACKGROUND

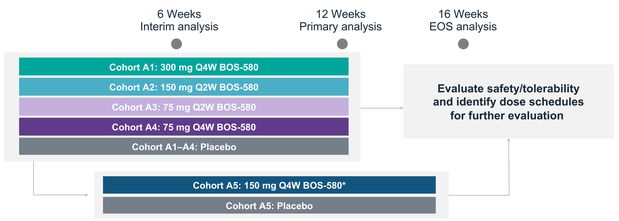
- BOS-580 is a long-acting highly engineered variant of human fibroblast growth factor 21 (FGF21) fused to human IgG1-Fc with an extended half-life of 21 days, enabling once-monthly dosing and is being developed for the treatment of metabolic dysfunction-associated steatohepatitis (MASH).
- MASH patients show extensive changes in the liver and blood lipidome, suggesting that perturbations in lipid metabolism may play a key role in the pathogenesis of this disease contributing to oxidative stress, inflammation and cell death.
- We evaluated changes in the circulating lipidome in patients with phenotypic MASH after 12 weeks of treatment with BOS-580 in a Phase 2a, Part A study (BOS-580-201).

AIMS

- Compare the circulating lipidome of phenotypic MASH patients to that of a healthy control population.
- Profile changes in the circulating lipidome in MASH patients treated with once-monthly or bi-weekly subcutaneous doses of BOS-580 over 12 weeks.
- Characterize changes in metabolomics advanced steatohepatitis fibrosis (MASEF) score[1], a novel composite biomarker to identify at-risk MASH patients, after 12 weeks of BOS-580 treatment.

STUDY DESIGN AND METHODS

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



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

- 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)

Once-monthly BOS-580 treatment over 12 weeks resulted in significant reductions in liver fat content, markers of liver injury and fibrosis, and numerically improved markers of metabolic health in patients with phenotypic MASH.

*6 of 15 subjects received BOS-580 30 mg as first dose followed by BOS-580 150 mg Q4W.
This trial is registered with ClinicalTrials.gov, NCT04880031, and Part A is completed.
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.

Lipidomics

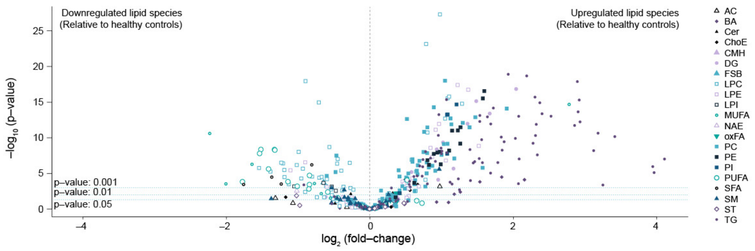
- In the Phase 2a, Part A study multiple dosing regimens of BOS-580 were evaluated with cohorts of 75 mg every 2 (Q2W) or 4 weeks (Q4W), 150 mg Q2W or Q4W, and 300 mg Q4W, or placebo.
- Serum samples for lipidomic profiling were collected from patients with phenotypic MASH at baseline and after 12 weeks of BOS-580 treatment. Metabolite extraction and analysis were performed at Rubio Metabolomics according to standard methods.
- A pre-existing profile derived from obese, healthy volunteers for comparison to our baseline population was provided by Rubio Metabolomics.

MASEF Scores

- MASEF scores[1] were calculated based on 12 lipids, body mass index (BMI), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) for each patient at baseline and after 12 weeks of BOS-580 treatment.

RESULTS

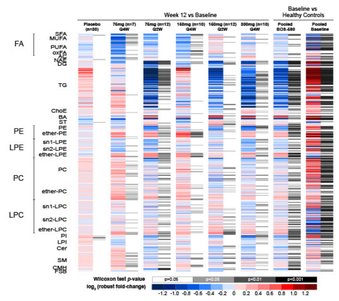
Distinct Differences in the Circulating Lipid Profiles of Patients with Phenotypic MASH Compared to Obese, Otherwise Healthy Controls



AC, acyl carnitines; BA, bile acids, Cer, ceramides; ChoE, cholesterol esters; CMH, monohexosylceramides; DG, diglycerides; FSB, free sphingoid bases; LPC, lysophosphatidylcholines; LPE, lysophosphatidylethanolamines; LPI, lysophosphatidylinositols; MUFA, monounsaturated fatty acids; NAE, N-acyl ethanolamines; oxFA, oxidized fatty acids; PC, phosphatidylcholines; PE, phosphatidylethanolamines; PI, phosphatidylinositols; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; SM, sphingomyelins; ST, sterols; TG, triglycerides.

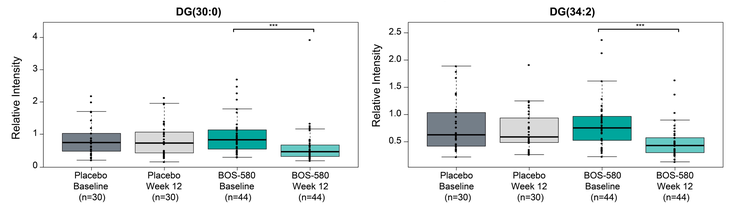
- A comparison of the lipid profile of baseline samples from phenotypic MASH patients in this study to that from obese, otherwise healthy volunteers (mean BMI = 35.8, NAS = 0) identified numerous differences.
- Baseline samples were enriched in triglycerides, bile acids and diacyl-phospholipids but showed lower levels of non-esterified fatty acids and some lysophosphatidylcholines.
- Of interest, lipotoxins such as certain diglycerides and ceramides were also elevated in baseline samples, consistent with such molecules potentially playing a role in the pathogenesis of MASH.[3, 4]

BOS-580 Treatment Leads to Significant Changes in the Circulating Lipidome in Phenotypic MASH Patients



- This heatmap shows the relative expression of lipid species after 12 weeks of BOS-580 treatment compared to baseline.
- Each color-coded line represents a single lipid species: red indicates increased abundance at Week 12 and blue denotes decreased abundance at Week 12; statistical significance of $\log_2$ fold-change is shown in the adjacent column.
- Each pair of columns represents 1 cohort from the study (or placebo); in the penultimate pair of columns on the right, the data from all cohorts was pooled (excluding one that was minimally effective, cohort A4) to increase statistical power.
- The final pair of columns on the right compares the lipid composition of the baseline samples from this study to those from an obese, otherwise healthy, control group.
- BOS-580 treatment leads to overall improvement and partial normalization of the circulating lipidome (reductions in elevated levels of di- and triglycerides, bile acids; increases in lysosphophatidylcholines).

BOS-580 Treatment Leads to Significant Decreases in Serum Lipotoxins

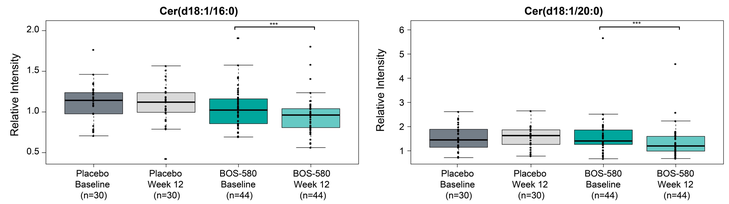


***p < 0.001.
All BOS-580 treatment cohorts were pooled (excluding cohort A4) for these analyses.

Diglycerides

- Diglycerides (DG) are lipotoxic molecules and have been related to both MASH and hepatic insulin resistance.[3,4] Elevated levels of these lipotoxins are thought to play key roles in the pathology of MASH.
- DG levels are elevated in the serum of phenotypic MASH patients, and are reduced by BOS-580 treatment, suggesting at least a partial normalization of the lipidome with respect to these species by this treatment.

RESULTS (cont'd)

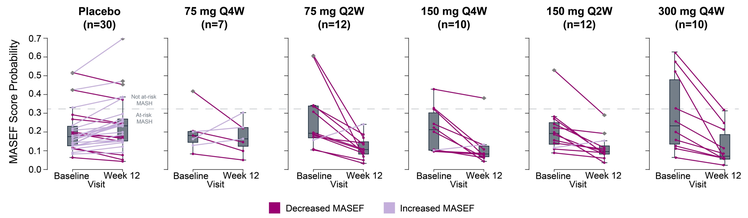


***p < 0.001.
All BOS-580 treatment cohorts were pooled (excluding cohort A4) for these analyses.

Ceramides

- Ceramides are known drivers of lipotoxicity in MASH, leading to cell injury, recruitment and activation of inflammatory cells, and trigger stellate cell activation and collagen deposition.[5]
- BOS-580 treatment leads to significant decreases in ceramide species in the circulating lipidome, suggesting potential clinical benefit in MASH patients.

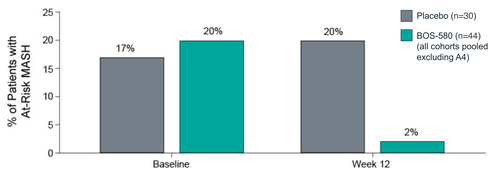
Improved MASEF Scores After 12 Weeks of BOS-580 Treatment



- MASEF score is a composite biomarker calculated from a panel of 12 lipids, BMI, AST and ALT to identify patients with at-risk MASH (NAS ≥ 4, fibrosis ≥ F2) using a cutoff of 0.33 as shown by the dashed grey line on the above graphs[1]. The lipid components of the score include 2 triglycerides, 5 glycerophosphocholines, 1 cholesteryl ester, 1 ceramide, and 3 sphingomyelins.
- 88% of patients treated with BOS-580 achieved reduced scores after 12 weeks, whereas the scores declined in 33% of patients in the placebo group.

Improved MASEF Risk Classification After 12 Weeks of BOS-580 Treatment

Change in % of Patients Identified with At-Risk MASH After 12 Weeks of BOS-580 Treatment



- Patients with at-risk MASH (NAS ≥ 4, fibrosis ≥ F2) were identified using MASEF 1-score cutoff of 0.33.[1]
- The at-risk population in the placebo group grew from 17% at baseline to 20% after 12 weeks.
- The at-risk population in the BOS-580 group declined from 20% at baseline to 2% after 12 weeks.

CONCLUSION

- In the Phase 2a, Part A study, we identified distinct differences in the circulating lipid profiles of phenotypic MASH patients compared to obese, otherwise healthy controls.
- BOS-580 treatment of these patients led to extensive changes in the circulating lipidome, including decreased levels of saturated fatty acids and triglycerides; notably, these samples also had lower levels of lipotoxic molecules such as diglycerides and ceramides, suggesting that the potential beneficial effects of BOS-580 may be mediated in part by reducing lipotoxic molecules in MASH patients.
- Treatment with once-monthly and bi-weekly doses of BOS-580 reduced MASEF scores in phenotypic MASH patients after 12 weeks and improved MASEF risk classification, suggesting potential clinical benefit with a reduction of at-risk MASH in this patient population.

REFERENCES

1. Noureddin M, et al. *Hepatology*. 2024;79(1):135-148. **2.** Loomba R, et al. EASL Congress 2023; June 21-24, 2023; Vienna, Austria. **3.** Neuschwander-Tetri BA. *Hepatology*. 2010;52(2):774-778. **4.** Peterson MC and Shulman GI. *Trends Pharmacol Sci*. 2017;38(7):649-665. **5.** Hajduch E, et al. *J Clin Med*. 2021;10(4):792.

ACKNOWLEDGEMENTS

The development of this poster was supported by Boston Pharmaceuticals. We thank Rubio Metabolomics for their assistance and Eric Svensson for his advice during the early stages of this work. Editorial support provided by Peloton Advantage, LLC, an OPEN Health company, and was funded by Boston Pharmaceuticals.

DISCLOSURES

GB, AC, JL, and TO: employees and/or shareholders of Boston Pharmaceuticals.

DOI: 10.3252/pso.eu.EASL2024.2024