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BOS-580, an Investigational FGF21 Analog, Improved Markers of Glycemic Control and Liver Steatosis in a Diabetic Sub-Population Enrolled in a Phase 2a Double-Blind, Placebo-Controlled Study in Patients with Phenotypic NASH

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INTRODUCTION

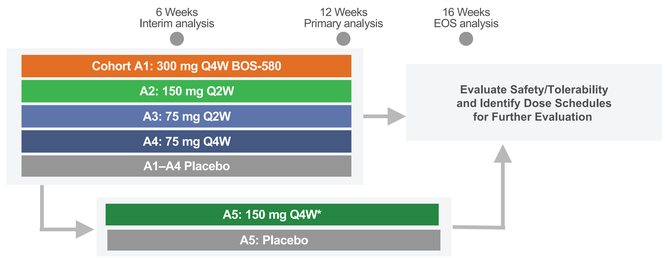
- BOS-580 is a long-acting, highly engineered variant of human fibroblast growth factor 21 (FGF-21) fused to human IgG1-Fc being developed for the treatment of non-alcoholic steatohepatitis (NASH).
- Several studies have shown that individuals with nonalcoholic fatty liver disease (NAFLD) are at a higher risk for developing type 2 diabetes (T2D).[1] Two-thirds of people with T2D are also affected by NAFLD.[2]
- FGF-21 improves glucose homeostasis by increasing peripheral insulin sensitivity and enhancing peripheral glucose disposal.[3]
- We examined the effect of BOS-580 treatment on glycemic control biomarkers and liver steatosis reduction in diabetic sub-populations enrolled in a Phase 2a study (BOS-580-201).

AIM

- To examine changes in various glycemic control biomarkers and liver steatosis in diabetic sub-populations of patients with phenotypic NASH treated with once-monthly or bi-weekly subcutaneous doses of BOS-580 over 12 weeks.

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)

- 102 patients with phenotypic NASH were randomized into 5 dosing groups as shown and administered BOS-580 or PBO for 12 weeks.
- Data from the dosing cohorts were pooled, excluding one that was minimally effective (Cohort A4).
- Glycemic markers were assessed in diabetic sub-populations defined by baseline HbA1c values:
  - HbA1c <5.7% (normal)
  - HbA1c ≥5.7% and <6.5% (pre-diabetics)*
  - HbA1c ≥6.5% (diabetics)
- Overall results for Part A have been previously presented at EASL 2023, Vienna, Austria.[4]

*This sub-population is composed of prediabetics (~65%) plus well-controlled diabetics on anti-diabetic medication (~35%).

RESULTS

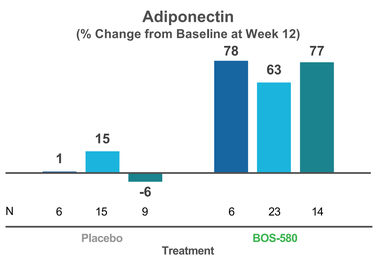
Baseline Characteristics and Treatment Response Summary

	Placebo			BOS-580 (Pooled Treatment Groups)*		
Baseline Characteristics (Mean)	**HbA1c <5.7% n=6**	**HbA1c ≥5.7% and <6.5% n=17**	**HbA1c ≥6.5% n=10**	**HbA1c <5.7% n=7**	**HbA1c ≥5.7% and <6.5% n=26**	**HbA1c ≥6.5% n=15**
Age, years	48.7	50.5	63.0	49.9	50.6	57.3
Female, %	50.0	41.2	30.0	14.3	61.5	53.3
BMI, kg/m^2	37.2	37.5	35.3	34.2	36.2	38.0
LSM, kPa	8.55	8.06	8.02	8.11	8.37	8.11
HFF, %	15.4	16.6	23.7	20.6	21.0	24.4
AST, IU/L	40.3	25.1	30.8	29.4	33.5	40.3
ALT, IU/L	70.7	37.5	38.4	46.7	49.0	55.7
HbA1c, %	5.60	5.92	7.40	5.39	5.92	7.39
HOMA-IR	6.23	4.11	8.81	2.92	6.32	8.24
Adiponectin (µg/L)	5250	3796	5635	3267	4469	3747
Diagnosed with diabetes, %	0	35.3	90.0	14.3	34.6	86.7
BOS-580 Treatment Responses (Mean)**						
Adiponectin change from baseline to week 12, %	1.0	15.3	−6.1	77.8	62.7	77.1
C-peptide change from baseline to week 12, %	−5.3	9.4	−11.2	−20.2	−7.6	−19.3
HbA1c change from baseline to week 12	0.11	0.01	−0.05	−0.10	−0.11	−0.45
HbA1c normalization: patients with HbA1c<5.7% at week 12, %	33.3	13.3	0	85.7	36.4	0
HFF change from baseline to week 12, %	−12.51	0	0.93	−66.15	−60.27	−57.00
HFF responders: subjects with ≥50% reduction at week 12, %	16.7	0	0	85.7	75.0	64.3

*BOS-580-201 study is composed of 2 separate parts: A & B. Data from 4 of 5 treatment groups from completed Part A, excluding one that was minimally effective (75 mg Q4W), were pooled.
**Based on LS mean with treatment and baseline value effects in the model performed on the modified full analysis set (ie, patients with at least 1 dose of study drug and an MRI at baseline and Week 6 or Week 12).

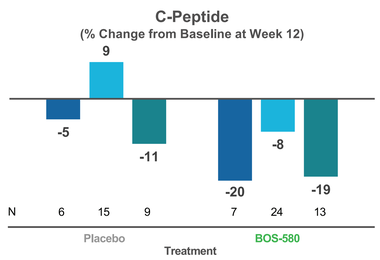
Normal (HbA1c <5.7%) Pre-Diabetic (HbA1c ≥5.7% and <6.5%) Diabetic (HbA1c ≥6.5%)

Adiponectin Upregulation in Response to BOS-580



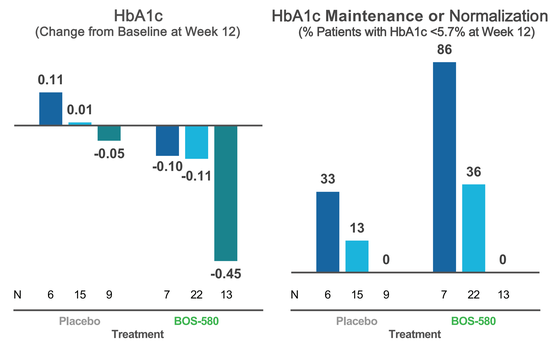
- Adiponectin, a pharmacodynamic marker of FGF21 receptor activation, is strongly upregulated in normal, pre-diabetic, and diabetic sub-populations with phenotypic NASH treated with BOS-580, indicating that all 3 sub-populations show similar FGF21 signaling pathway activation.

Reductions in C-Peptide After BOS-580 Treatment



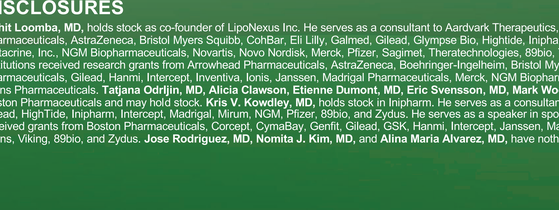
- C-peptide, a surrogate for insulin production, showed generally greater reductions in all diabetic sub-populations after BOS-580 treatment compared to placebo.
- Reductions in C-peptide levels among BOS-580–treated subjects indicate an improvement in insulin resistance.

Glycated Hemoglobin Levels After BOS-580 Treatment



- HbA1c levels declined in all 3 sub-populations after BOS-580 treatment, with a numerically greater improvement in the diabetic sub-population compared to the normal and pre-diabetic groups.
- BOS-580 improved the percentage of patients who maintained or achieved HbA1c normalization (<5.7%) after 12 weeks of treatment compared to placebo in the normal and pre-diabetic sub-populations.
- 31% of patients in the diabetic sub-population reduced HbA1c to <6.5% after BOS-580 treatment, compared to only 11.1% in the placebo group (data not shown).

Changes in Hepatic Fat Fraction in Patients Treated with BOS-580



- The normal, prediabetic, and diabetic sub-populations showed very similar decreases in hepatic fat fraction, as measured by MRI-PDFF, after 12 weeks of BOS-580 treatment.
- ≥64% of patients in each sub-population were super responders (ie, ≥50% HFF reduction) after 12 weeks of treatment.
- BOS-580 was as effective in reducing HFF in patients on BOS-580 plus anti-diabetic medication compared to patients on BOS-580 alone (data not shown).

CONCLUSIONS

- BOS-580 treatment improved insulin resistance as shown by the reduction of C-peptide levels across all diabetic sub-populations.
- The diabetic sub-population showed a numerically greater reduction in HbA1c levels compared to the prediabetic and normal sub-populations.
- BOS-580 treatment improved the percentage of patients who maintained or achieved HbA1c normalization (<5.7%) in the normal and pre-diabetic sub-populations and led to a greater fraction of patients in the diabetic sub-population who were able to reduce HbA1c to <6.5% compared to the placebo group.
- BOS-580 treatment achieved similar reductions in HFF and super responder rates across diabetic sub-populations compared to placebo.
- No cases of hypoglycemia were observed in patients treated with BOS-580 in this study as previously reported.[4]
- Given the prevalence of T2D in NASH patients, the role of BOS-580 in improving glycemic control is particularly relevant.

DISCLOSURES

Rohit Loomba, MD, holds stock as co-founder of LipoNexus Inc. He serves as a consultant to Aardvark Therapeutics, Altimmune, Anylam/Regeneron, Amgen, Arrowhead Pharmaceuticals, AstraZeneca, Bristol Myers Squibb, CohBar, Eli Lilly, Galmed, Gilead, Glympse Bio, Hightide, Inipharm, Intercept, Inventiva, Ionis, Janssen Inc., Madrigal, Metacrine, Inc., NGM Biopharmaceuticals, Novartis, Novo Nordisk, Merck, Pfizer, Sagimet, Theratechnologies, 89bio, Terns Pharmaceuticals, and Viking Therapeutics. His institutions received research grants from Arrowhead Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Bristol Myers Squibb, Eli Lilly, Galectin Therapeutics, Galmed Pharmaceuticals, Gilead, Hanmi, Intercept, Inventiva, Ionis, Janssen, Madrigal Pharmaceuticals, Merck, NGM Biopharmaceuticals, Novo Nordisk, Pfizer, Sonic Incytes, and Terns Pharmaceuticals. **Tatjana Odrljin, MD, Alicia Clawson, Etienne Dumont, MD, Eric Svensson, MD, Mark Woodruff, MD,** and **Gerard Bain, PhD,** are employees of Boston Pharmaceuticals and may hold stock. **Kris V. Kowdley, MD,** holds stock in Inipharm. He serves as a consultant to Boston Pharmaceuticals, CymaBay, Enanta, Genfit, Gilead, HighTide, Inipharm, Intercept, Madrigal, Mirum, NGM, Pfizer, 89bio, and Zydus. He serves as a speaker in sponsored lectures to AbbVie, Gilead, and Intercept. He has received grants from Boston Pharmaceuticals, Corcept, CymaBay, Genfit, Gilead, GSK, Hanmi, Intercept, Janssen, Madrigal, Mirium, Novo Nordisk, NGM, Pfizer, Pliant, Terns, Viking, 89bio, and Zydus. **Jose Rodriguez, MD, Nomita J. Kim, MD,** and **Alina Maria Alvarez, MD,** have nothing to disclose.

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