KB195, a Novel Glycan, Modulates Ammonia Metabolism in Healthy Subjects and in Microbiome Samples Collected From Patients With Urea Cycle Disorders

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INTRODUCTION

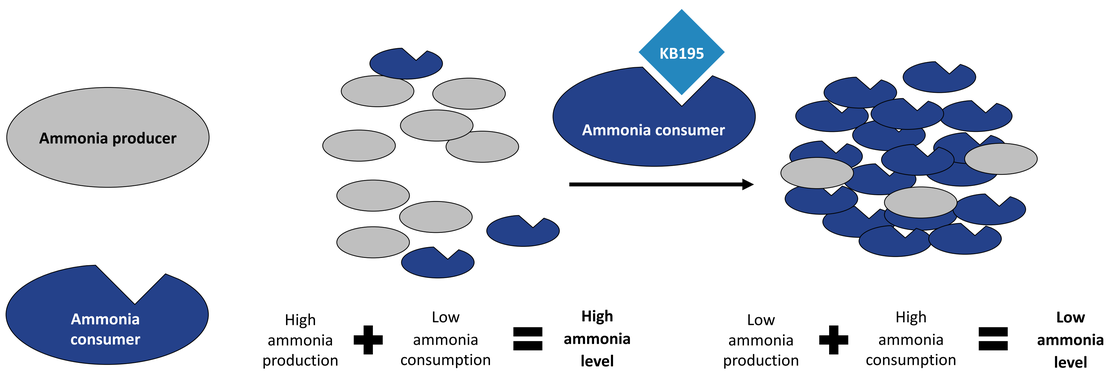
The gut microbiome plays a significant role in the production and consumption of ammonia, which is central to the pathogenesis of urea cycle disorders (UCD). Existing therapies, such as lactulose, reduce blood ammonia but are poorly tolerated and not very efficient.

We sought to develop Microbiome Metabolic Therapies (MMT™) that are synthetic, novel oligosaccharide compositions (glycans) to reduce net ammonia production by the gut microbiome with good tolerability. MMTs are related to a class of compounds that is "Generally Recognized as Safe," or GRAS, or are determined to be GRAS, based on their history of safe human exposure when utilized for particular uses as food substances, and are commonly accepted as safe by regulators for use in food. This classification allows for the collection of early human data; for UCD this human data is collected in a nitrogen metabolism model system.

An *ex vivo* screening platform was established to collect data on the effect of glycans as MMTs. Via this platform, fecal samples from healthy human microbiomes were incubated with more than 300 glycans. Levels of microbiota-derived metabolites, including ammonia, were measured.

One of the top-performing glycans from the screen was KB195. One proposed mechanism of action for KB195 is to change the composition of bacterial species in the gut to modulate the level of metabolites, including ammonia (Figure 1).

FIGURE 1. ONE PROPOSED MECHANISM OF ACTION FOR KB195



OBJECTIVES

The objectives of the study were to assess the ability of KB195 to

- Reduce ammonia levels in fecal microbiome samples from patients with UCD in an *ex vivo* assay.
- Reduce ammonia levels in a clinical food study in healthy human subjects. Safety and tolerability were also evaluated.

METHODS

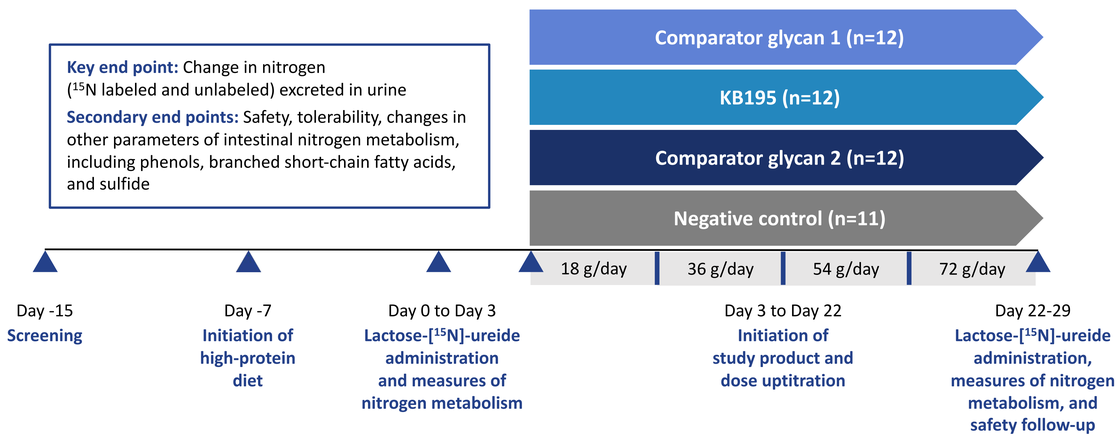
***Ex vivo* assay**

- KB195 and 19 other glycans were tested in an *ex vivo* assay with 12 fecal microbiome samples from patients with UCD.

Clinical food study

- A controlled, randomized, double-blind clinical food study of KB195 was conducted in healthy human subjects.
- Subjects were between 18 and 50 years of age, with a body mass index (BMI) of 20 to 40 and no history of gastrointestinal (GI) conditions (inflammatory bowel disease, irritable bowel syndrome, GI malignancy) or GI-related medications or supplements (including probiotics, fiber supplements, and bismuth).
- As perturbations in blood ammonia after protein challenge are difficult to measure in healthy subjects, a model system using a lactose-[^{15}N]-ureide tracer was used. After screening and initiation of a high-protein diet, subjects were given a standard oral dose of lactose-[^{15}N]-ureide as a tracer for bacterial nitrogen metabolism. In this model, ^{15}N excretion in the urine was a surrogate marker of nitrogen metabolism in the gut; a reduction in urinary ^{15}N is consistent with a reduction in net ammonia production by the gut microbiome.
- Subjects were administered KB195 (n=12) or 1 of 3 comparator compounds: comparator glycan 1 (n=12), comparator glycan 2 (n=12), or negative control (n=11). Subjects were again given lactose-[^{15}N]-ureide at the end of the 21-day study period (Figure 2).

FIGURE 2. STUDY DESIGN

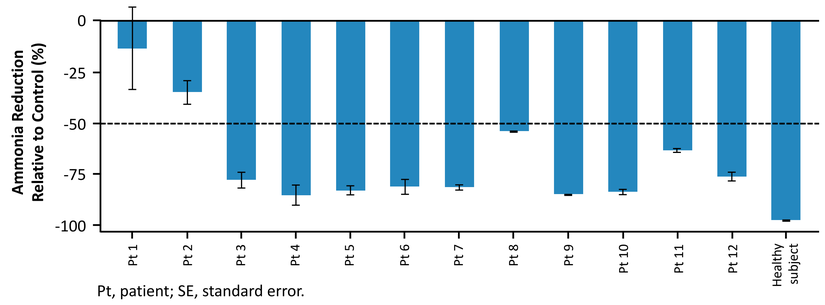


Safety was reported as treatment-emergent adverse events (TEAEs). In addition to standard adverse event reporting, we used sensitive measures to assess GI tolerability including the GI Tolerability Questionnaire (GITQ) and the Bristol Stool Scale (BSS). The GITQ assesses the severity and frequency of GI symptoms, including nausea, vomiting, abdominal cramping, gas/flatulence, and reflux on 4-point scales (range is 0 to 64). Two additional questions were added to this questionnaire to assess frequency and urgency of bowel movements. Subjects were expected to complete the questionnaire daily from 1 to 3 days after screening until the end of the study. The BSS assesses stool consistency (range is 0 to 7; scores of 6 or 7 were scored as diarrhea); subjects scored all bowel movements according to the scale for the duration of the study.

RESULTS

In the *ex vivo* assay with 12 fecal microbiome samples from patients with UCD, KB195 reduced ammonia levels in all samples and showed reduction >50% compared with control in 83% (10/12) of the microbiome samples tested (Figure 3).

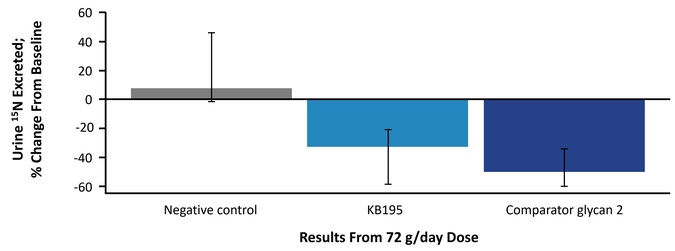
FIGURE 3. AMMONIA LEVELS: KB195 RELATIVE TO CONTROL (MEAN ± SE)



Pt, patient; SE, standard error.

Forty-seven subjects were randomized in the clinical food study. The study population was 49% male and 77% white, with a mean age of 35 years and a mean BMI of 27. All 47 subjects completed the study. The study also included an additional comparator glycan arm (comparator glycan 1). Operational challenges resulted in interruptions in the glycan 1 dosing schedule. As such, the incomplete glycan 1 arm data are not reported. After ingestion of KB195, subjects showed a decrease in total urinary ^{15}N excretion compared with the negative control (P=0.0126; Figure 4), independent of the microbiome structure at baseline.

FIGURE 4. DECREASE IN ^{15}N EXCRETION (KB195 VS NEGATIVE CONTROL)



Overall, there were no safety signals (Table 1). Most TEAEs were mild in severity; no subject discontinued due to a TEAE. Of the 3 subjects who reported TEAEs that were considered moderate in severity, none were deemed related to study product. All adverse events resolved or were improving over the 7-day follow-up period after the end of study product consumption. There were no clinically relevant abnormal laboratory values.

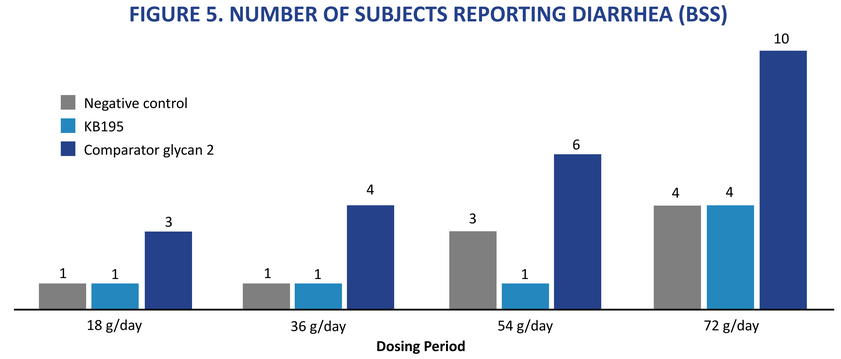
TABLE 1. TEAEs IN THE CLINICAL FOOD STUDY

	KB195 (n=12)	Comparator glycan 2 (n=12)	Negative control (n=11)	Overall (N=35)
Total number of TEAEs	17	35	10	62
Subjects reporting ≥1 TEAE, No. (%)	4 (33.3)	6 (50.0)	4 (36.4)	14 (40.0)
Maximum TEAE intensity, No. (%)				
Mild	3 (25.0)	6 (50.0)	7 (63.6)	16 (45.7)
Moderate	2 (16.7)	1 (8.3)	0	3 (8.6)
Severe	0	0	0	0

No subjects had a TEAE leading to discontinuation or death; no subjects reported serious TEAEs.

Tolerability of KB195 was comparable to that of negative control at all doses in the GITQ (data not shown) and BSS (Figure 5). Treatment with KB195 resulted in fewer subjects reporting diarrhea compared with comparator glycan 2.

FIGURE 5. NUMBER OF SUBJECTS REPORTING DIARRHEA (BSS)



CONCLUSIONS

The MMT KB195 reduced net ammonia production in *ex vivo* fecal microbiome samples from healthy individuals and patients with UCD, reduced gut microbiome-derived ammonia in healthy subjects, and was well tolerated. Future clinical studies are planned to investigate the activity and tolerability of KB195 for the reduction of ammonia levels in patients with UCD and other diseases that cause hyperammonemia. A clinical food study in patients with UCD (NCT03797131) is currently recruiting and a Phase 2 study is also planned.

ACKNOWLEDGEMENTS & REFERENCES

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Reference: Data on file. Kaleido Biosciences Inc.

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