Identification of Novel Glycans That Target Gut Microbiota-Associated Ammonia Production

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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 hepatic encephalopathy [1]. Existing therapies, such as a lactulose, reduce blood ammonia levels but are poorly tolerated.

We sought to develop Microbiota-Metabolites Therapies (MMTs) that mimic endogenous microbiota-associated 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," based on their history of safe human exposure when used for particular uses as food substances, and are commonly accepted as safe by regulators for use in food.

OBJECTIVES

The objective of the study was to assess the ability of KB195 to:

- Reduce ammonia levels in fecal microbiome samples from patients with hepatic encephalopathy.

METHODS

In the ex vivo assay with 25 fecal microbiome samples from patients with hepatic encephalopathy, KB195 reduced ammonia levels in 25% (20/25) of samples, and in 74% (14/19) of samples, KB195 resulted in greater reductions in ammonia levels than lactulose (Figure 3).

RESULTS

In the ex vivo assay with 30 fecal microbiome samples from patients with hepatic impairment, KB195 reduced ammonia levels in 75% (22/29) of samples, and in 100% (30/30) of samples, KB195 resulted in greater reductions in ammonia levels than lactulose (Figure 4).

CONCLUSIONS

These studies with KB195 have informed our understanding of the activity and tolerability of MMTs in the reduction of ammonia levels. Future clinical studies aim to show improved management of patients with hyperammonemia, including those with urea cycle disorders and hepatic encephalopathy. A phase 2 clinical trial in patients with urea cycle disorders is planned to assess the ability of KB195 to achieve the primary endpoint of ammonia reduction. A clinical food study to assess the effect of another MMT (BS1574) on reducing ammonia levels in patients with well-compensated cirrhosis is also underway (NCT03359196).

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