An Open-Label, Single-Arm Clinical Study to Evaluate Safety and Tolerability of KB195, a Novel Glycan, in Patients With Urea Cycle Disorders

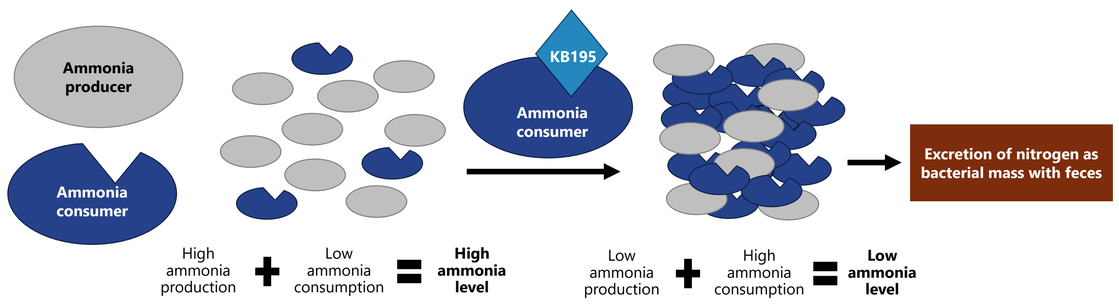
Johannes Häberle[1], Amy Thomas[2], Elizabeth Sawicki[2], Michael Mahowald[2], Brian Meehan[2], Angela Beccarelli[1], Kathrin Weber[1], Margaret J. Koziel[3]

[1]University Children's Hospital Zurich, Division of Metabolism and Children's Research Center, Zurich, Switzerland; [2]Kaleido Biosciences Inc, Lexington, Massachusetts, [3]Former Employee of Kaleido Biosciences, Inc., Lexington, Massachusetts.

INTRODUCTION

- The gut microbiome plays a significant role in the production and consumption of ammonia. Ammonia is central to the pathogenesis of urea cycle disorders (UCD). Existing therapies, such as phenylbutyrates and benzoate, reduce blood ammonia levels but may not be sufficient alone or may be toxic if the blood values are too high.
- Novel synthetic glycans (Microbiome Metabolic Therapies [MMT]™) may reduce net gut-associated ammonia production and have been shown to have good tolerability. MMTs are related to a class of compounds that is generally recognized as safe (GRAS) or determined to be GRAS based on a history of safe human exposure. This class is commonly accepted by regulators as safe for use in food. KB195 is GRAS, which enables rapid advancement into human clinical studies.
- An ex vivo screening platform was established to investigate the effect of MMTs on microbiota-mediated ammonia production. In this screen, KB195 was among the MMTs that mediated the greatest magnitude of reduction in ammonia levels. KB195 has several potential non-mutually exclusive mechanisms of action, including through enriching for bacteria that act as net ammonia consumers at the expense of those that act as net ammonia producers (Figure 1).
- In a prior controlled, randomized, double-blind clinical study in healthy human subjects, KB195 reduced gut microbiome-derived nitrogen metabolism and was generally well tolerated.

FIGURE 1. PROPOSED MECHANISM OF ACTION FOR KB195



OBJECTIVES

The objectives of this open-label clinical study were:

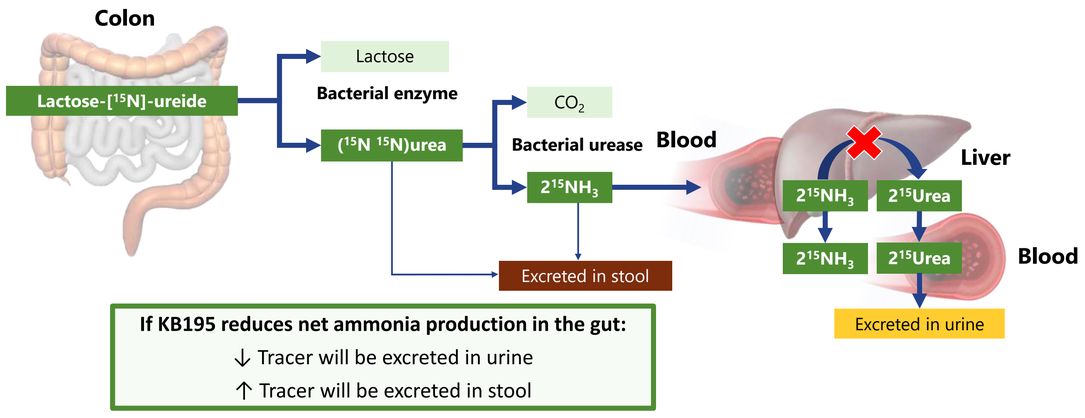
- To evaluate safety and tolerability of KB195 in patients with well-controlled UCD
- To explore the effect of KB195 on measures of nitrogen metabolism in patients with UCD

METHODS

Study Design

- An open-label single-center clinical study was conducted with patients with well-controlled UCD.
- Patients ≥14 years of age with no history of N-acetylglutamate synthase deficiency, liver transplant, and any medical condition unrelated to UCD that can cause hyperammonemia were included.
- Patients received a lactose-[^{15}N]-ureide tracer, followed by KB195 orally twice daily for 21 days, and then received another dose of the tracer at the end of the dosing period (Figures 2 and 3).
- To minimize potential gastrointestinal tolerability issues, KB195 was dosed by weight and titrated up to the final dose over 4 periods.
- Blood, urine, and stool samples were collected for safety laboratories as well as biomarkers of gut nitrogen metabolism.
- Safety and tolerability were assessed through adverse event reporting as well as gastrointestinal tolerability questionnaires.

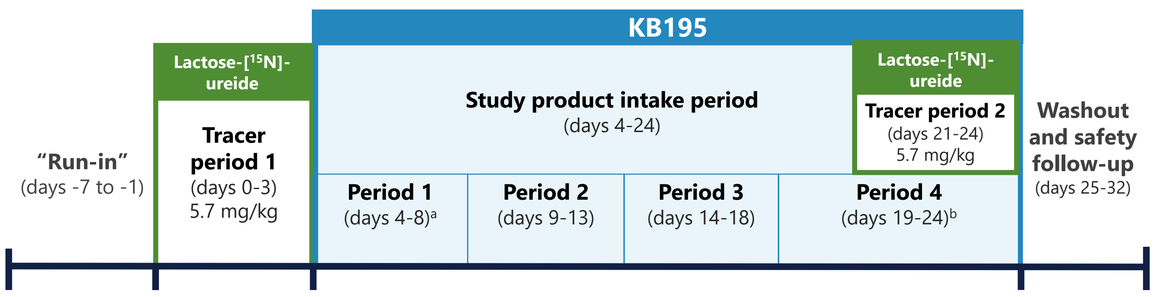
FIGURE 2. LACTOSE-[^{15}N]-UREIDE TRACER



Lactose-[^{15}N]-ureide tracer is used as a marker of nitrogen metabolism. This stable isotope tracer is not metabolized by human enzymes but is a substrate for a bacterial enzymes in the gut, which separates the urea and lactose portions. Bacterial urease then hydrolyzes urea to ammonia.

FIGURE 3. STUDY DESIGN, KB195 DOSING, AND STUDY OUTCOMES

- Screening occurred at day -15
- Safety assessments were gathered on day 25 (at last clinic visit)



[a]Day 4: first intake taken under supervision at clinic.
[b]Day 24: last intake taken in morning.

KB195 Daily Dosing by Weight, grams

Weight 50 kg or less	10.5 (5.25 2x/day)	21 (10.5 2x/day)	31.5 (15.75 2x/day)	42 (21 2x/day)
Weight >50 kg	18 (9 2x/day)	36 (18 2x/day)	54 (27 2x/day)	72 (36 2x/day)

Measured Outcomes

- Change in labeled and total nitrogen excretion in urine
- Change in labeled and total nitrogen excretion in stool
- Change in plasma NH_3 levels
- Assessment of gastrointestinal tolerability questionnaire score
- Bristol stool form scale score
- Overall tolerability
- Stool frequency and urgency

Note as of Dec 11, 2019: This is the poster as presented at SSIEM (Sept 4, 2019). Errors were subsequently found in the reporting of 15N tracer data; updated data are included here.

- The mean percent decrease (n=3) previously reported for urinary ^{15}N was 15% (SD 24) vs.45% (SD 48) (corrected). The median decrease is 68%.
- The mean percent increase (n=3) previously reported for ^{15}N excretion in stool was 39% (SD 27) vs 365% (SD 554) (corrected); The median increase is 115%.
- The changes do not change the clinical interpretation

RESULTS

TABLE 1. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

	Age, y; Sex	UCD Genetic Defect	Time of Diagnosis	Current Interventions	Plasma NH_3 Level	Additional Medical History	Daily Dose of KB195, g
Patient 1	17; M	ASL	Infant	Diet, arginine	Normal	–	72
Patient 2	42; F	ASL	Newborn	Diet, arginine	Normal	Obesity, arterial hypertension	72
Patient 3	18; F	ASS	Infant	Diet, arginine	Normal	Constipation (resolved)	72
Patient 4	14; F	OTC	Before 6 y	Diet, arginine, sodium phenylbutyrate	Normal	–	42

ASL, argininosuccinate lyase deficiency; ASS, argininosuccinate synthetase deficiency; F, female; M, male; OTC, ornithine transcarbamylase deficiency.

- 4 subjects with well-controlled UCD were included, and all completed the study.
  - All patients received KB195 dose by weight and reached the maximal dose.
- Sampling was incomplete in 2 patients.
  - Patient 1 had incomplete sampling of urine collection in tracer period 1 and was excluded from analysis of nitrogen and ^{15}N excretion in urine.
  - Patient 4 had incomplete sampling of fasting blood draw at tracer period 2 and was excluded from evaluation of fasting ammonia level.

SAFETY AND TOLERABILITY

TABLE 2. ADVERSE EVENTS WERE MILD

	Daily Dose of KB195, g	Preferred Term	Severity	Relationship to Study Product
Patient 1	72	• No events reported	–	–
Patient 2	72	• Flatulence	Mild	Possibly related
Patient 3	72	• Flatulence	Mild	Possibly related
Patient 4	42	• Gastrointestinal sounds abnormal • Flatulence • Headache	Mild Mild Mild	Possibly related Possibly related Unlikely related

- There were no serious treatment-emergent adverse events and no treatment discontinuations due to adverse events

Additional Tolerability Measures

- Through measurement of Bristol Stool Scale (BSS) scores, treatment with KB195 caused no increase in diarrhea.
- Maximum stool frequency stayed consistent from baseline to follow-up, whereas flatulence increased in 2 of the patients during the intake period.

FIGURE 5. OVERALL TOLERABILITY OF KB195 WAS GOOD

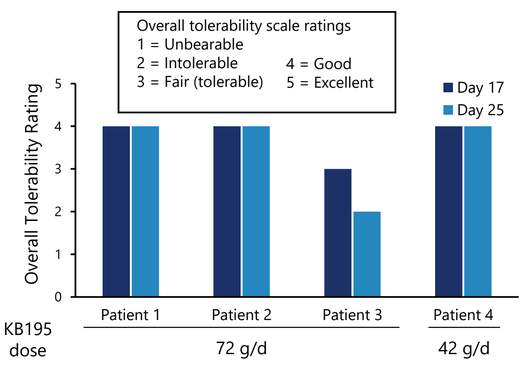
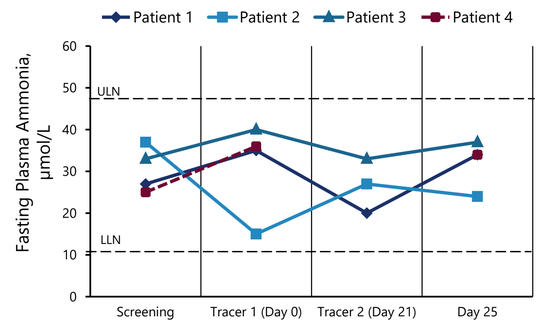


FIGURE 4. PLASMA NH_3 LEVELS WERE CONTROLLED AT BASELINE AND REMAINED WITHIN THE NORMAL RANGE[a]

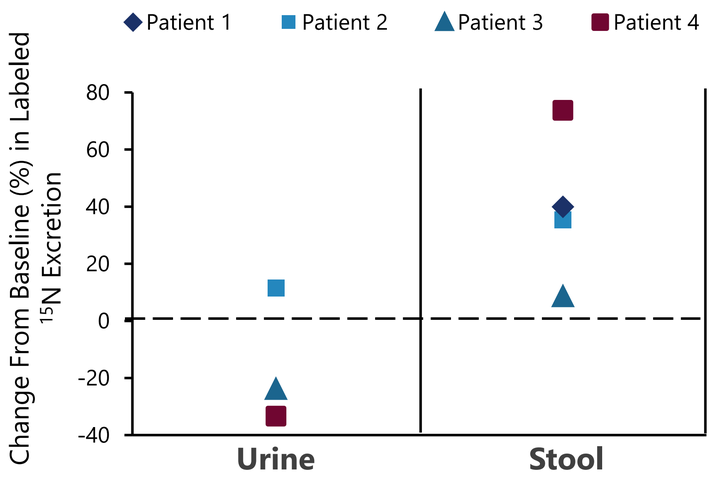
- Mean change in NH_3 level (screening to day 25) was -11%.



[a]There was no blood draw for patient 4 at tracer period 2.
LLN, lower limit of normal; ULN, upper limit of normal.

NITROGEN METABOLISM

FIGURE 6. EXCRETION OF ^{15}N LABELED NITROGEN GENERALLY INCREASED IN STOOL AND DECREASED IN URINE[a]



↓ Tracer was excreted in urine (2 of 3 evaluable patients)

↑ Tracer was excreted in stool (4 of 4 patients)

- Mean decrease of urinary ^{15}N excretion was ~ 15% (SD 24)
- Mean increase of ^{15}N excretion in stool was ~ 39% (SD 27)

[a]Patient 1 was excluded from urine analysis due to missing urine collection hours 0 to 24.

CONCLUSIONS

- Similar to previous results in healthy subjects, KB195 was well tolerated with no clinically significant safety signals observed in 4 patients with UCD receiving 21 days of dosing.
- There were only mild treatment-emergent adverse events and no treatment discontinuations due to adverse events.
- NH_3 levels were controlled at baseline and, as expected, remained at normal levels throughout the study.
- There was a general increase in ^{15}N in stool and decrease in urine, suggestive of KB195 activity in reducing nitrogen metabolism by bacterial-derived urease in the gut microbiome.
- A global phase 2 clinical trial in a larger number of patients with inadequately controlled UCD is ongoing.

ACKNOWLEDGEMENTS AND REFERENCES

Acknowledgements: Frank Henke, Melody Lashlee, and Ruth Thieroff-Ekerdt for contributions to this work. ETHOS Health Communications provided editorial support.

Reference: Data on file. Kaleido Biosciences Inc.

Conflict of interest:

Commercial: Johannes Häberle, participation in the study presented in the abstract. Angela Beccarelli and Kathrin Weber, have nothing to disclose.
Company details: Johannes Häberle, Kaleido Consultant; Amy Thomas, Kaleido Employee and owns stock; Elizabeth Sawicki, Kaleido Employee and owns stock; Michael A. Mahowald, Kaleido Employee and owns stock; Brian Meehan, Kaleido Employee and owns stock; Margaret J. Koziel, former Kaleido Employee.

Scan me

Scan to download poster

SSIEM I Society for the Study of Inborn Errors of Metabolism. 3-6 September 2019. Rotterdam, the Netherlands.