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Results of a Phase 2 Randomized Controlled Trial of ALLN-177 in Patients with Secondary Hyperoxaluria

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References: 1) Curhan and Taylor, *Kidney Int*. 2008; **2)** Borghi, *N Eng J Med*. 2002

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Hyperoxaluria (HOx) and Kidney Damage

- Oxalate is an end-product of carbohydrate and amino acid metabolism, and it is also absorbed from the diet. There is obligatory renal excretion of the metabolic and dietary oxalate load.
- HOx is a serious metabolic disorder that often leads to kidney stone formation and kidney damage. With declining kidney function, systemic oxalate deposition may occur.
- Primary HOx is a rare genetic disorder associated with very high UOx levels. Secondary HOx is caused by excess absorption of oxalate from the gastrointestinal (GI) tract due to an underlying GI disorder (enteric), or due to unknown causes (idiopathic). Subjects with Enteric HOx may have urine oxalate (UOx) levels that approach those seen in primary HOx.
- Published data suggest that reducing UOx by ≥ 20% may reduce kidney stone recurrence by more than 25%.[1,2]
- There are no approved pharmacological therapies for HOx. Current management consists of recommendations to restrict dietary oxalate and increase calcium and fluid intake, but these may be difficult to sustain, especially in Enteric HOx.

ALLN-177: Crystalline Formulation of Oxalate Decarboxylase

- ALLN-177 is a first-in-class oral enzyme therapeutic that specifically targets oxalate
  - Rapidly degrades oxalate within the GI tract
  - No detectable systemic absorption
  - Reduces GI oxalate absorption, thereby decreasing UOx excretion

ALLN-177 Phase 2 Study 713

Study Objectives and Design

- Phase 2, multi-center, randomized, double-blind, placebo-controlled study (Figure 1)
- Evaluate safety and efficacy of ALLN-177
- Randomization 1:1 to ALLN-177 or Placebo, with randomization stratified by Screening UOx level
- 24-hour urine collections were obtained at specified intervals
- Diet recalls were conducted via telephone interview by trained Diet Recall Center staff

Figure 1: Phase 2 Study Design

Screening 24 days	Baseline and 28-day Treatment Period					Safety Follow-Up
Key Entry Criteria	Baseline (3 days)	Week 1	Week 2	Week 3	Week 4	7 days
• Adults with secondary HOx • UOx ≥ 50 mg/24h • GFR ≥ 45 mL/min/1.73 m²	Randomized 1:1	ALLN-177 (7,500 u) 3x per day with meals/snacks				
		Placebo 3x per day with meals/snacks				
	2 x UOx	2 x UOx	1 x UOx	1 x UOx	3 x UOx	
Continued recommended diet and medications for management of kidney stone risk factors. Diet recalls conducted to determine dietary oxalate intake.						

Key Efficacy Endpoints

- **Primary Endpoint:** Mean change in UOx from Baseline to Week 4
- **Additional Endpoints:**
  - Mean and percent change from Baseline to Time-Weighted Average (TWA) UOx across Weeks 1-4 (mg/24h)
  - Percent change in UOx from Baseline to Week 4

Analytical Methods

- **Efficacy analyses** were based on the modified intent-to-treat (mITT) population, and included restricted maximum likelihood-based mixed-effects model repeated measures analysis (MMRM) and analysis of covariance (ANCOVA). Models adjusted for Baseline UOx excretion and site effect.
- **Subgroup analyses:** By type of secondary HOx (enteric and idiopathic) for selected efficacy endpoints.
- **Safety:** Treatment-emergent adverse events (TEAEs).

Subject Characteristics

- 67 subjects were randomized and treated; 18 (27%) had Enteric HOx (Table 1)
- Baseline characteristics were similar in the two treatment groups for All Subjects
- Compared with All Subjects, subjects in the Enteric HOx subset had higher UOx levels at Baseline and relatively lower dietary oxalate intake
- The main underlying diagnosis among the 18 subjects with Enteric HOx was bariatric surgery (13; 72.2%); 3 (16.7%) subjects had inflammatory bowel disease, and 2 (11.1%) had pancreatic insufficiency

Table 1: Subject Characteristics at Baseline

Baseline Parameter (mean [SD])	All Subjects (N = 67)		Enteric HOx Subjects (N = 18)	
	ALLN-177 (n = 32)	Placebo (n = 35)	ALLN-177 (n = 11)	Placebo (n = 7)
Age (years)	58 (11.2)	59 (11.7)	63 (12.0)	65 (6.6)
Males, n (%)	24 (75)	24 (68.8)	7 (63.6)	1 (14.3)
BMI (kg/m²)	33.88 (7.65)	33.09 (6.55)	32.64 (8.00)	37.32 (7.02)
UOx (mg/24h)	71.81 (41.35)	66.81 (38.22)	104.39 (56.04)	101.54 (70.42)
Diet recall oxalate (mg/day)	291.71 (257.16)	241.58 (175.45)	248.18 (204.91)	148.94 (75.54)

Safety

- All ALLN-177 treated subjects completed the study; 2 Placebo subjects discontinued due to TEAEs
- All TEAEs were mild or moderate intensity; no deaths, serious AEs, or severe AEs reported
- GI TEAEs were the most common; incidence was lower in ALLN-177 than Placebo
  - All Subjects: 15.6% ALLN-177 vs. 40% Placebo
  - Enteric HOx subjects: 27.3% ALLN-177 vs. 42.9% Placebo
- Related TEAEs occurred less frequently in ALLN-177 subjects than Placebo subjects
  - All Subjects: 3 in ALLN-177 group and 8 in Placebo group had related TEAEs:
    - ◊ ALLN-177: GI disorders (n = 2) and muscle spasms (n = 1)
    - ◊ Placebo: GI disorders (n = 7) and dermatitis (n = 1)
  - Enteric HOx subset: 1 subject in each treatment group had a related TEAE:
    - ◊ ALLN-177: flatulence (n = 1)
    - ◊ Placebo: dyspepsia (n = 1)

Table 2: Summary of Treatment Emergent Adverse Events in Overall and Enteric HOx Subjects n (%) (Safety Population)

Category	All Subjects (N = 67)		Enteric HOx Subjects (N = 18)	
	ALLN-177 (n = 32)	Placebo (n = 35)	ALLN-177 (n = 11)	Placebo (n = 7)
TEAE[1]	16 (50%)	22 (62.9%)	6 (54.5)	5 (71.4)
Related TEAE	3 (9.4%)	8 (22.9%)	1 (9.1)	1 (14.3)
AEs Leading to Study Drug Withdrawal	0	2 (5.7%)[2]	0	0

1. TEAEs are AEs with onset at or after first dose of study drug through 7 days after last dose of study drug, or AEs increasing in severity or relationship at or after start of treatment through 7 days after last dose of study drug.
2. Two placebo-treated subjects withdrew from study drug, one after nearly 4 weeks of treatment due to nausea (considered not related) and another due to hives/dermatitis with onset 3 days after starting study drug (considered possibly related).

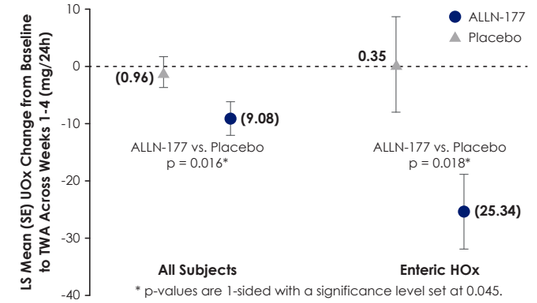
Efficacy

Table 3: Summary of Treatment Differences between ALLN-177 vs. Placebo in Change from Baseline in 24-hour UOx Excretion

UOx Change	All Subjects (N = 67)		Enteric HOx Subjects (N = 18)	
	ALLN-177 vs. Placebo	90% CI	ALLN-177 vs. Placebo	90% CI
Change from Baseline to Week 4				
Mean (mg/24h)	-6.35	-14.84, 2.14	-16.45	-47.53, 14.62
Percent	-15.81	-27.86, -3.77	-36.25	-71.43, -1.06
Change from Baseline to TWA across Weeks 1-4				
Mean (mg/24h)	-8.13	-14.34, -1.92	-25.69	-45.09, -6.29
Percent	-14.23	-24.87, -3.59	-39.15	-65.46, -12.85

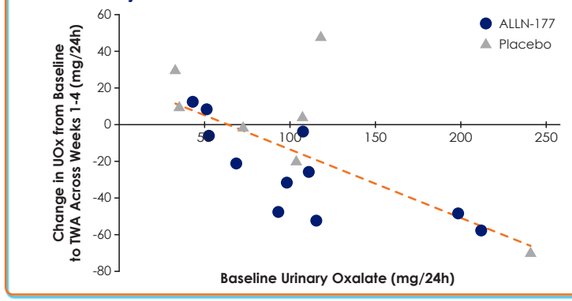
Note: Table 3 presents LS means, LS mean differences (ALLN-177 vs. Placebo) and 90% CI.

Figure 2: LS Mean UOx Change from Baseline to Post-Baseline TWA (mg/24h)



* p-values are 1-sided with a significance level set at 0.045.

Figure 3: Change in UOx from Baseline vs. Baseline UOx Excretion in Subjects with Enteric HOx



- Study drug compliance was high, and comparable between treatment groups: 97.4% ALLN-177 vs. 94.9% Placebo groups
- In the All Subjects group, various analyses consistently demonstrated greater reduction in 24-hour UOx excretion with ALLN-177 compared with Placebo (Table 3):
  - LS mean change from Baseline to Week 4, ALLN-177 vs. Placebo: -8.75 mg/24h vs. -2.40 mg/24h (p = 0.160)
  - LS mean change from Baseline to TWA UOx across Weeks 1-4, ALLN-177 vs. Placebo (Figure 2): -9.08 mg/24h vs. -0.96 mg/24h (p = 0.016)
  - 40.6% ALLN-177 vs. 8.6% Placebo had ≥ 20% decrease from Baseline to TWA UOx, with an OR of 9.59 (90% CI 2.21, 41.61; p = 0.006)
- In the Enteric HOx group, the magnitude of reduction in 24-hour UOx with ALLN-177 compared with Placebo was consistently greater compared with All Subjects (Table 3):
  - LS mean change from Baseline to Week 4, ALLN-177 vs. Placebo: LS mean = -21.31 mg/24h vs. -4.86 mg/24h (p = 0.184)
  - LS mean change from Baseline to TWA UOx across Weeks 1-4, ALLN-177 vs. Placebo (Figure 2): -25.34 g/24h vs. +0.35 mg/24h (p = 0.018)
  - 63.6% ALLN-177 vs. 14.3% Placebo had ≥ 20% decrease from Baseline to TWA UOx, with an OR of 9.35 (90% CI 0.59, 148.60; p = 0.092)
- In the Enteric HOx group:
  - Magnitude of reduction correlated with Baseline UOx level (Figure 3; dotted line fit to all data)
  - Change in UOx was not driven by changes in dietary oxalate; change from Baseline to Week 4 in dietary oxalate ALLN-177 vs. Placebo: 13.41 mg/day vs. -2.72 mg/day
- There were no substantive changes in any of the other 24h urine stone risk parameters

Discussion / Conclusions

- ALLN-177 in subjects with Enteric HOx:
  - Substantially reduced UOx in this high-risk population
  - Was well-tolerated, with no drug-related serious or severe AEs, and no discontinuations of study drug due to AE
  - Specific to oxalate, with minimal-to-no changes in non-oxalate urine parameters
- The underlying physiology of Enteric HOx corresponds to ALLN-177's mechanism of action of degrading oxalate in the GI tract and reducing intestinal oxalate absorption
- Mean UOx across Weeks 1-4 (time-weighted average) is a relevant assessment of efficacy, as it better reflects physiologic benefit (impact over a period of time, rather than at a single time point) and it is less sensitive to variability
- ALLN-177 has the potential to address a significant unmet medical need for treatments to reduce UOx excretion in subjects with Enteric HOx

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