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

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Hyperoxaluria (HOx) and Kidney Damage
- Urinary oxalate is the predominant component of calcium oxalate and calcium oxalate monohydrate, and it is also observed from the diet. There is a obligatory renal excretion of the metabolic and dietary oxalate load.

- HOx is a severe 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 a growing 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 idiopathic HOx.

- HOx is a serious metabolic disorder that often leads to kidney stone formation and kidney damage. With substantial renal excretion of the metabolic and dietary oxalate load, these patients are at high risk for kidney stone formation. With obligatory renal excretion of the metabolic and dietary oxalate load.

- Published data suggest that reducing UOx by ≥ 20% may reduce kidney stone recurrence by more than 25%.

**ALLN-177: Crystalline Formulation of Oxalate Decarbonylase**
- ALLN-177 is a novel and enzyme therapeutical: Specifically targets oxalate.
  - Rapidly degrades oxalate within the GI tract
  - Substantially reduces UOx in this high-risk population

**Study Objectives and Design**
- Phase 3 multicenter, randomized, double-blind, placebo-controlled study (Figure 1)
  - Evaluate safety and efficacy of ALLN-177
  - Randomization 1:1 to ALLN-177 or Placebo
  - Randomization stratified by screening oxalate level
  - 24 hour urine collections were obtained at specified intervals
  - Diet recalls were conducted via telephone interview by trained Diet Recall Center staff

**Subject Characteristics**
- Of 67 subjects randomized and treated; 18 (27%) had Enteric HOx (Table 1)

**Study Key Investigators**
- Was well-tolerated, with no drug-related serious or severe AEs reported
- Substantially reduced UOx in this high-risk population

**Subject Characteristics**
- Of 67 subjects randomized and treated; 18 (27%) had Enteric HOx (Table 1)

- Baseline characteristics were similar in the two treatment groups for All Subjects

- The main underlying diagnosis among the 10 subjects with enteric HOx was bariatric surgery (n = 3; 27.3%), 5 (45.5%) subjects had inflammatory bowel disease, and 2 (18.2%) had pancreatic insufficiency

**Efficacy**
- Study drug compliance was high, and comparable between treatment groups: 97.4% ALLN-177 vs. 94.9% Placebo patients

- In the All Subjects group, various analyses consistently demonstrated greater reduction in 24 hour UOx excretion with ALLN-177 compared with Placebo (Table 3): (1) mean change from Baseline to 4 weeks, ALLN-177 vs. Placebo: -8.75 ± 25.34 mg/24h (p = 0.016); (2) mean change from Baseline to TWA UOx across Weeks 1-4: ALLN-177 vs. Placebo: -25.69 ± 25.34 mg/24h (p = 0.016). ALLN-177 also had a 0.25 decrease from Week 1 (p = 0.016)

- In the Enteric HOx group, the magnitude of reduction in 24 hour UOx with ALLN-177 compared with Placebo was consistently greater than with Placebo (Table 3)

**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

**Trial Design**
- Randomized 1:1 to ALLN-177 or Placebo
- Randomization stratified by screening oxalate level
- 24-hour urine collections were obtained at specified intervals
- Diet recalls were conducted via telephone interview by trained Diet Recall Center staff

**Table 1: Subject Characteristics at Baseline**

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

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

**Figure 1: Phase 2 Study Design**

- Baseline and 28-day Treatment Period

- Safety Population

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

**Figure 3: Change in UOx from Baseline vs. Baseline Urinary Oxalate (mg/24h)**

**Discussion & Conclusions**
- ALLN-177 in subjects with Enteric HOx:
  - Substantially reduced UOs in this high-risk population
  - Was well-tolerated, with no drug-related serious or severe AEs, and no discontinuations of study drug due to AEs
  - 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 UOs across Weeks 1-4 (time-weighted average) is related to measurement of efficacy, as it better reflects physiologic benefit (impact over a period of time, rather than at a single time point) and typically is less sensitive to variability

- ALLN-177 has the potential to address a significant unmet medical need for treatments to reduce UOs with limited clinical effects