Baseline Characteristics from BONAPH1DE: a Global, Observational, Longitudinal Study of Patients with Primary Hyperoxaluria Type 1

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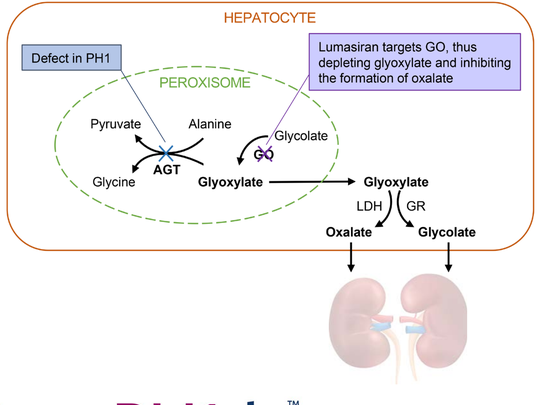
Conclusions

- Demographic and clinical characteristics at enrollment from BONAPH1DE show lumasiran use across all ages and the full range of CKD progression, ranging from normal kidney function to patients undergoing dialysis
- Ongoing enrollment and longitudinal data collection are expected to enable future analyses of the real-world safety and effectiveness of lumasiran and provide insights into the evolving clinical management in PH1

Introduction

- Lumasiran is an RNAi therapeutic approved in the European Union for the treatment of PH1 in all age groups[1] and the United States for the treatment of PH1 to lower urinary and plasma oxalate levels in pediatric and adult patients[2] (**Figure 1**).
  - PH1 is a rare, potentially life-threatening disease associated with recurrent kidney stones, progressive kidney disease, and multiorgan damage from systemic oxalosis.[3-5]
  - Historically, treatment options for PH1 have been limited and have had suboptimal outcomes.[4,6]
- Clinical trial data support the efficacy and safety of lumasiran in patients of all ages and varying levels of disease severity.[7-13]
- There is a need to understand factors that influence the course of disease, including novel and emerging treatments.
- BONAPH1DE (NCT04982393; EUPAS43242) is an ongoing observational study to collect data to inform the clinical management of PH1.
- The purpose of this analysis is to describe the baseline demographic and clinical characteristics of patients at enrollment in BONAPH1DE.

Figure 1. Mechanism of Disease in PH1 and Lumasiran Mechanism of Action[7,8,14,15]



BonaPH1de™

Methods

Study Design and Population

- We examined the treatment history of the patients to ascertain whether they were ever treated with lumasiran or not in the entire registry for data collected up to the data cutoff date.
  - Anticipated PH1 treatment history included lumasiran treated, untreated, treated with other approved therapies for PH1, liver or combined liver-kidney transplanted, and kidney-only transplanted.
- The study design and eligibility criteria are described in **Figure 2.**

Figure 2. BONAPH1DE Study Design and Eligibility Criteria

Study Design

- BONAPH1DE is a global, multicenter, prospective, observational, longitudinal study
- Study size: Approximately 200 patients with PH1 will be enrolled in the study
- Patients with PH1 are managed and treated per routine clinical practice; no specific treatments, visits, or procedures are required

Eligibility

- Inclusion criteria
  - Documented diagnosis of PH1, per physician's determination
  - Patient consent
- Exclusion criteria
  - Currently enrolled in a clinical trial for any investigational agent

Duration: At Least 7 Years From Start of Study

Data Sources and Collection

- The study database includes data from clinical and laboratory assessments that are part of routine management of PH1.
- Data collection includes patient and disease characteristics, laboratory assessments, clinical outcomes, and safety outcomes of interest.
- The following were collected at baseline (enrollment): demographics; PH1 diagnosis (including genetic testing, if available); PH1 manifestations and symptoms at diagnosis; PH1 management and treatment; and clinical laboratory results, if available (urinary oxalate, plasma oxalate, serum creatinine, liver transaminases, INR, prothrombin time, electrolytes, urine glycolate, and urine creatinine).
- Following enrollment, study data are collected prospectively at routine clinical encounters or by referencing the medical record, and at least once every 12 months (**Figure 3**); the study also includes retrospective data collection.
- The overall number of patients with PH1 was not prespecified.

Figure 3. Prospective Data Collection

Clinical Presentation and Management

PH1 manifestations and symptoms
PH1 management & treatment, including lumasiran treatment through the cutoff date
Clinical laboratory results if available: Urinary oxalate, plasma oxalate, serum creatinine, transaminases, INR, prothrombin time, electrolytes, urine glycolate, and urine creatinine

Concomitant medications, including immunosuppressants for transplant and pain medications
PH1-related health resource utilization measures
PROs
Diagnosed comorbidities

Safety Assessments

Safety outcomes of interest
- Hepatic events
- Hospitalization (including cause)
- Mortality (including cause)

Pregnancy and birth outcomes (including history)
Infant outcomes at birth
Lactation and infant follow-up data through first year of life
AEs from the time of informed consent (in lumasiran-exposed patients only)

- **Retrospective data collection:** Variables collected prospectively (except demographics, PROs, lactation information, and AEs) are also collected retrospectively from the medical records with a chart review of up to 5 years relative to baseline (enrollment).

Results

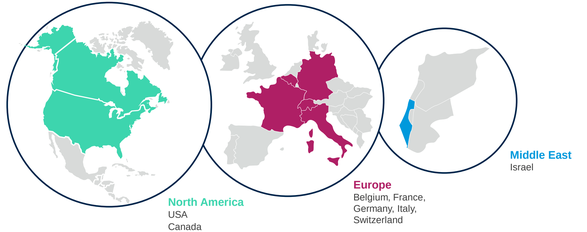
- From December 13, 2021, to January 30, 2024, 98 patients from 8 countries were enrolled (**Figure 4**).

Figure 4. BONAPH1DE Study Status (as of January 30, 2024)

Enrollment started December 13, 2021

Number of sites activated: 21

Projected enrollment: 200 patients



- Excluding 14 patients with liver transplant prior to enrollment, 72 patients had a treatment history with lumasiran, 9 patients were never treated with lumasiran, and 3 patients did not have lumasiran treatment history available (**Table**).
- At enrollment, 33% of lumasiran-treated patients reported pyridoxine use and 33% had a pyridoxine-responsive PH1 variant.
- Compared with patients never treated with lumasiran, lumasiran-treated patients tended to be younger, diagnosed earlier, less likely to report history of kidney stones (44% vs 78%) or kidney transplant (4% vs 22%), and more likely to have nephrocalcinosis (43% vs 22%).
- The majority of lumasiran-treated patients (56%) had normal kidney function or stage 2 CKD.
- Among all 84 enrolled patients without a history of liver transplant, 20 (24%) had stage 4 or 5 CKD; 18 of them were treated with lumasiran.

Table. Demographic and Clinical Characteristics at Enrollment[a]

Demographic and Clinical Characteristics	Lumasiran-Treated Patients (N=72)	Patients Never Treated with Lumasiran (N=9)
Age at consent/assent, mean (range), years	15.3 (0.3, 64.0)	40.6 (22.0, 68.0)
Age at consent/assent, n (%)		
<2 years	10 (14)	0
≥2 to <12 years	24 (33)	0
≥12 to <18 years	15 (21)	0
≥18 to ≤45 years	18 (25)	7 (78)
>45 to ≤65 years	5 (7)	1 (11)
>65 years	0	1 (11)
Age at diagnosis, mean (range), years	8.3 (0.0, 57.0)	22.9 (2.0, 45.0)
Male, n (%)	38 (53)	3 (33)
Region, n (%)		
North America	18 (25)	4 (44)
Europe	41 (57)	5 (56)
Middle East	13 (18)	0
AGXT genotype[b], n (%)		
PR/PR	0	1 (11)
PR/-	24 (33)	4 (44)
-/-	47 (65)	4 (44)
Not available	1 (1)	0
Years from diagnosis to enrollment, mean (range)	7.4 (0.0, 37.2)	17.3 (1.1, 35.7)
Type of treatment at enrollment, n (%)		
Hyperhydration	21 (29)	0
Crystallization inhibitors	23 (32)	0
Pyridoxine (vitamin B6)	24 (33)	6 (67)
Low oxalate diet	5 (7)	0
Dialysis	9 (13)	2 (22)
Lumasiran	66 (92)	0
Other	9 (13)	1 (11)
Not reported	4 (6)	0
eGFR, n (%), mL/min/1.73m²		
≥90	28 (39)	0
60 to <90	12 (17)	1 (11)
45 to <60	6 (8)	2 (22)
30 to <45	2 (3)	1 (11)
15 to <30	7 (10)	0
0 to <15	11 (15)	2 (22)
Not collected at enrollment	6 (8)	3 (33)
Kidney transplant, n (%)	3 (4)	2 (22)
Nephrocalcinosis, n (%)	31 (43)	2 (22)
History of kidney stones, n (%)	32 (44)	7 (78)

Note: As of the data cutoff date, lumasiran treatment history is not available for 3 patients.
[a]Excluding 14 patients with liver transplant prior to enrollment.
[b]PR (pyridoxine-responsive): M_000030.3(AGXT):c.508G>A (p.Gly170Arg) or NM_000030.3(AGXT):c.454T>A (p.Phe152Ile); -: Any other mutation.

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Abbreviations: AE, adverse event; AGT, alanine–glyoxylate aminotransferase; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; INR, International Normalized Ratio; GO, glycolate oxidase; GR, glyoxylate reductase; LDH, lactate dehydrogenase; mRNA, messenger ribonucleic acid; PAS, post authorization study; PH1, primary hyperoxaluria type 1; PRO, patient-reported outcome; RNAi, ribonucleic acid interference.

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