LEADER 3D: Leveraging Natural History and Registry Data to Inform Endpoint Selection for a Rare Disease

Lumasiran (Oxlumo)

Before reading this case study, please refer to the LEADER 3D Case Study User Guide as an informational resource. FDA recognizes that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases and that development challenges are often greater with increasing rarity of the disease. The small population affected by a rare disease presents additional considerations that must be addressed and also calls for appropriate flexibility. **Please note this case study is not intended or designed to provide specific strategies for obtaining product approval.** Rare disease drug development is not one-size-fits-all. The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and must therefore be assessed on a case-by-case basis.

Learning Objectives

After reading this case study you will:

- Have a greater understanding of how natural history and registry data can inform endpoint selection in rare disease drug development programs.
- Be aware of how a biomarker-based surrogate endpoint can be considered fit-for-purpose when supported by pathophysiologic, epidemiologic, and observational evidence.
- Be familiar with the relevant FDA guidance documents that discuss concepts covered within this case study (e.g., natural history studies, endpoint selection)

To access FDA guidance documents for rare disease drug development organized by topic, please scan this QR code.

Case Study Summary

This case study examines how the Applicant engaged with the U.S. Food and Drug Administration (FDA) to use natural history (NHS) and registry data to inform biomarker-based endpoint selection and support the approval of lumasiran (Oxlumo) for the treatment of primary hyperoxaluria type 1 (PH1) in patients with relatively preserved kidney function. For additional details on this case study, please refer to the Integrated Review for lumasiran.

Lumasiran is a subcutaneously administered small interfering ribonucleic acid (siRNA) that inhibits the messenger RNA (mRNA) for glycolate oxidase (GO), thereby reducing hepatic oxalate production. This drug represents the first pharmacologic treatment for PH1 to address the underlying metabolic cause of the disease.

FDA determined that reductions in 24-hour urinary oxalate excretion provided substantial evidence of effectiveness (SEE) to support approval. Urinary oxalate served as a biomarker-based surrogate endpoint that the Agency

Key Concept: Natural History Studies

A natural history study collects detailed clinical and patient information over time to understand how a disease develops and progresses. These studies often capture longitudinal data such as age at diagnosis, symptoms, medical images, laboratory results, and patient experiences. These data may be entered by patients, caregivers, clinicians, or researchers.

Natural history studies can play an important role in therapy development by helping researchers better characterize a disease and its progression. Data collected through these studies may reveal the range and severity of symptoms, how signs and symptoms change over time, and whether genetic or environmental factors influence disease presentation. Such information can help identify patient subgroups, establish diagnostic criteria, and highlight unmet medical needs within a disease community.

In addition to improving disease understanding, natural history data can support the development of clinical trials. These studies may help identify biomarkers, collect clinical and patient-reported outcomes, and inform the selection of outcome measures used in trials. Natural history studies can also help increase patient participation in clinical research and support the evaluation of therapies after regulatory approval.

concluded predicts benefit based on strong understanding of the disease's pathophysiology, findings from patient registries and disease natural history linking oxalate burden to kidney outcomes, and consistent treatment effects demonstrated in the pivotal clinical investigations.

Introduction to the Rare Disease: Primary Hyperoxaluria Type 1

PH1 is the most common and severe form of the primary hyperoxalurias, a group of rare genetic disorders of hepatic glyoxylate metabolism characterized by overproduction of oxalate, with an estimated prevalence of less than 5,000 cases in the United States.[1] PH1 results from biallelic mutations in the *AGXT* gene, which encodes the hepatic peroxisomal enzyme alanine-glyoxylate-aminotransferase (AGT). AGT deficiency leads to the accumulation of glyoxylate, which is rapidly converted to oxalate, a poorly soluble compound that combines with calcium to form calcium oxalate crystals (**Figure 1**, Panel B).

Patients typically present in childhood with recurrent kidney stones, nephrocalcinosis, and progressive renal impairment. As kidney function declines, the body's ability to excrete oxalate diminishes, resulting in systemic oxalosis, a debilitating condition that can cause cardiac arrhythmias, bone pain, fractures, gangrene, and blindness.

Current Treatment Options

At the time of the Applicant's new drug application (NDA) submission, there were no approved pharmacological treatments for PH1. Management strategies focused on preventing calcium oxalate crystallization through high fluid intake and supplementation with citrate and magnesium to increase oxalate solubility. Pyridoxine (vitamin B6) can reduce oxalate production in a subset of patients with specific *AGXT* mutations that lead to enzyme mislocalization; however, most patients derive limited or no benefit. For patients with advanced disease, liver transplantation (often combined with kidney transplantation) is the only curative therapy, though it carries substantial morbidity and the need for lifelong immunosuppression.

For more information on natural history studies, please refer to the NCATS Toolkit for Patient-Focused Therapy Development.

Key Concept: Surrogate Endpoints

A biomarker is a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions. There are many different types (e.g., molecular, histologic, radiographic, or physiologic characteristics), classes (e.g., efficacy response, safety, diagnostic), and uses of biomarkers (e.g., enrichment, predictive, prognostic), including use as outcomes for clinical trials to support drug and biologic approvals. A biomarker is not a direct measure of how an individual feels, functions, or survives.

A surrogate endpoint can be a biomarker intended to measure an outcome of interest in clinical trials that serves as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself but rather is expected to predict that clinical benefit based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.[2]

Surrogate endpoints are most appropriate when direct clinical endpoints are slow to manifest or impractical to measure, and when there is sufficient evidence (from epidemiology, pathophysiology, or prior clinical trials) to support that the surrogate endpoint can be relied upon to predict clinical benefit in a context of use.[3]

In the context of rare disease drug development, where clinical outcomes may not be feasible to measure within a trial of reasonable duration, surrogate endpoints may serve as the primary basis for establishing efficacy. Those considering using novel surrogate endpoints are encouraged to engage early with FDA (e.g., via INTERACT, pre-IND, or Type C meetings) to discuss the acceptability of the novel surrogate, identify gaps in evidence, and plan how to address these gaps before relying on the surrogate as the basis for product approval.

For more information on surrogate endpoints and their regulatory use, please refer to FDA's Surrogate Endpoint Resources for Drug and Biologic Development and Biologic Development and the BEST (Biomarkers, EndpointS, and other Tools) Resource.

[1] Primary hyperoxaluria type 1 web page (https://rarediseases.info.nih.gov/diseases/2835/primary-hyperoxaluria-type-1).

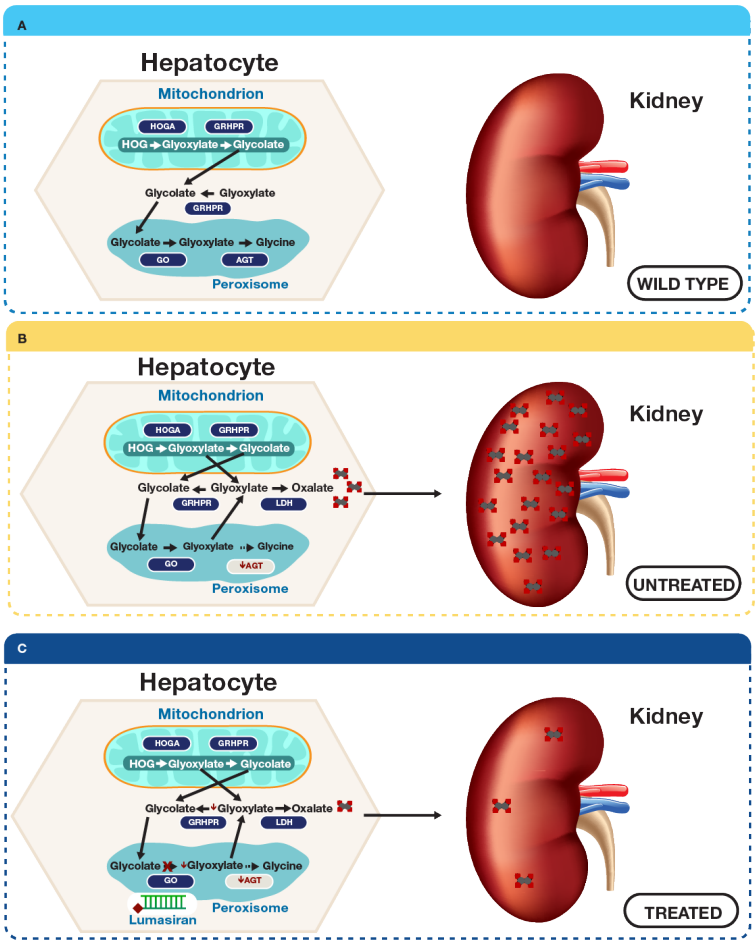
[2] BEST (Biomarkers, EndpointS, and other Tools) Resource web page (https://www.ncbi.nlm.nih.gov/books/NBK338448/).

[3] Surrogate Endpoint Resources for Drug and Biologic Development web page (https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development).

Lumasiran Mechanism of Action

Lumasiran acts by silencing hepatic expression of GO, which is encoded by the Hydroxyacid oxidase 1 (*HAO1*) gene. GO is upstream of AGT and is responsible for converting glycolate to glyoxylate (a precursor to oxalate) (**Figure 1**, Panel A). Lumasiran consists of a double-stranded siRNA conjugated to an N-acetyl-D-galactosamine (GalNAc) ligand, which facilitates targeted uptake by hepatocytes (liver cells) through asialoglycoprotein receptors. Once inside the hepatocyte, lumasiran binds to HAO1 mRNA, triggering its degradation via the RNA interference pathway. This inhibition decreases the conversion of glycolate to glyoxylate, thereby reducing oxalate production. Because glycolate is water-soluble and non-toxic, its accumulation does not produce adverse physiological effects (**Figure 1**, Panel C).

Figure 1: *Lumasiran Mechanism of Action*



FDA Guidance Corner

Rare Diseases: Natural History Studies for Drug Development *is a draft FDA guidance document which, when final, will represent the Agency's current thinking on topics in the case study. For up-to-date guidance documents please search* Guidance Documents for Rare Disease Drug Development | FDA.

In this case study, data from disease natural history and registries were critical to establishing a deep understanding of PH1 disease progression and linking urinary oxalate levels to kidney outcomes. This understanding enabled the selection of urinary oxalate as a fit-for-purpose biomarker-based surrogate endpoint.

Draft Guidance for Industry Rare Diseases: Natural History Studies for Drug Development (March 2019)

The natural history of a disease is traditionally defined as the course a disease takes in the absence of intervention in individuals with the disease, from the disease's onset until either the disease's resolution or the individual's death. A natural history study is a preplanned observational study intended to track the course of the disease. Its purpose is to identify demographic, genetic, environmental, and other variables (e.g., treatment modalities, concomitant medications) that correlate with the disease's development and outcomes. Natural history studies are likely to include patients receiving the current standard of care and/or emergent care, which may alter some manifestations of the disease. Disease registries are a frequent platform to acquire the data for natural history studies. Information obtained from a natural history study can play an important role at every stage of drug development, from drug discovery to the design of clinical investigations intended to support marketing approval of a drug and beyond into the postmarketing period.

A natural history study can help identify or develop biomarkers that can be diagnostic of the disease, prognostic of the disease's course, predictive of treatment response, or useful in guiding patient selection and dose selection in drug development programs. Natural history studies provide an opportunity to collect specimens and images that can be used in an analytical validation program. When robustly validated, these biomarkers can serve as surrogate endpoints in clinical trials.

Guidance for Industry Rare Diseases: Considerations for the Development of Drugs and Biological Products (December 2023)

The natural history of rare diseases is often poorly understood, and the need for prospectively designed, protocol-driven natural history studies initiated in the earliest drug development planning stages cannot be overemphasized. Although FDA does not require natural history studies, we advise sponsors to evaluate early the depth and quality of existing natural history knowledge to determine whether it is sufficient to inform their drug development programs.

Endpoint selection for a clinical investigation necessitates thorough understanding of the range and course of clinical manifestations associated with the disease. Sponsors can often obtain this knowledge, along with possible differences among patient subtypes, from a natural history study of the disease. Sponsors should select endpoints considering the objectives of each clinical investigation in the context of the overall clinical development program. Endpoint selection, especially considerations related to novel endpoints (that could be clinical outcomes or biomarkers as surrogate endpoints), is an important aspect of rare disease drug development. Sponsors are encouraged to engage early with the Agency to discuss endpoint development. Clinical investigations within a drug development program generally build upon the knowledge gained in early studies to guide the design and endpoint selection for later stages of development. Exploratory evidence from earlier phase clinical investigations may help inform the choice of dose and timing of endpoints. Leveraging data from natural history or registry-based studies of rare diseases may also help to identify clinically relevant endpoints as well as to examine the relationship between disease severity/progression and the biomarker changes (e.g., to provide initial support for a surrogate endpoint).

Data from Disease Natural History and Registries to Support Use of a Surrogate Endpoint

Since PH1 is a condition that progresses over many years, long-term registry and natural history data were instrumental in describing disease progression and identifying measurable indicators of kidney damage. In evaluating lumasiran, FDA relied on these data to characterize the progression of PH1 and to justify the selection of 24-hour urinary oxalate as the primary efficacy surrogate endpoint. Support for the use of urinary oxalate as a surrogate for clinical outcomes in PH1 was based primarily on (1) understanding PH1 pathophysiology, including the causal role of urinary oxalate in kidney stone formation, nephrocalcinosis, and loss of kidney function; (2) epidemiologic data from registries (e.g., Rare Kidney Stone Consortium, OxalEurope) demonstrating an association between urinary oxalate levels and decline in kidney function among patients with PH1, and (3) observational data from patients receiving pyridoxine therapy or liver transplantation, showing that reduction in urinary oxalate is associated with preservation of renal function.

Registry findings,[4,5] which helped define the natural history of PH1, consistently showed that patients with sustained elevations in urinary oxalate are more likely to develop nephrocalcinosis, kidney-stone recurrence, and a gradual loss of kidney function that can culminate in renal failure. Conversely, individuals with lower urinary oxalate levels tend to experience slower deterioration of kidney function. These observations established consistent epidemiologic evidence supporting correlation between the surrogate endpoint and the clinical outcome of interest (a relationship between oxalate burden and kidney outcomes), providing support for the use of urinary oxalate as a surrogate endpoint for PH1.

These data informed FDA's assessment of the lumasiran clinical program. Although the pivotal trials were of limited duration and could not directly assess outcomes such as kidney-stone events or renal failure, registry and natural history data provided important context for understanding how reductions in urinary oxalate would likely influence longer-term kidney health and reinforced the relationship between oxalate levels and renal outcomes in patients with

[4] Milliner DS, McGregor TL, Thompson A, et al, 2022, End points for clinical trials in primary hyperoxaluria, CJASN, 15(7):1056-1065.

[5] Hopp K, Cogal AG, Bergstralh EJ, et al, 2015, Phenotype-genotype correlations and estimated carrier frequencies of primary hyperoxaluria, J Am Soc Nephrol, 26(10):2559-2570.

PH1. Data derived from registries demonstrated a correlation between higher levels of urinary oxalate and risk of kidney failure in patients with PH1.[1] Together with the knowledge of PH1 pathophysiology, which links hepatic oxalate overproduction to excessive urinary oxalate excretion, calcium-oxalate crystal deposition in kidneys, kidney stones, and kidney injury, these data supported FDA's determination that:

- Sustained decreases in urinary oxalate in patients with PH1 and relatively preserved kidney function are likely to translate to clinical benefit;
- Urinary oxalate reduction represented a suitable surrogate endpoint for establishing treatment benefit in PH1 patients with relatively preserved kidney function.

This regulatory approach reflects recommendations outlined in FDA's Rare Diseases: Natural History Studies for Drug Development guidance document, which encourage the use of longitudinal observational data to identify biomarkers that capture disease progression and predict clinical outcomes. In the case of lumasiran, natural history and registry data filled critical evidence gaps, providing confidence that the magnitude of change in the concentration of the biomarker could predict benefit for clinical manifestations of the disease. Through this integration of registry evidence and mechanistic understanding, FDA concluded that urinary oxalate was an appropriate surrogate endpoint for assessing the effectiveness of lumasiran in a population where conventional clinical outcomes could not be measured within a trial of reasonable duration.

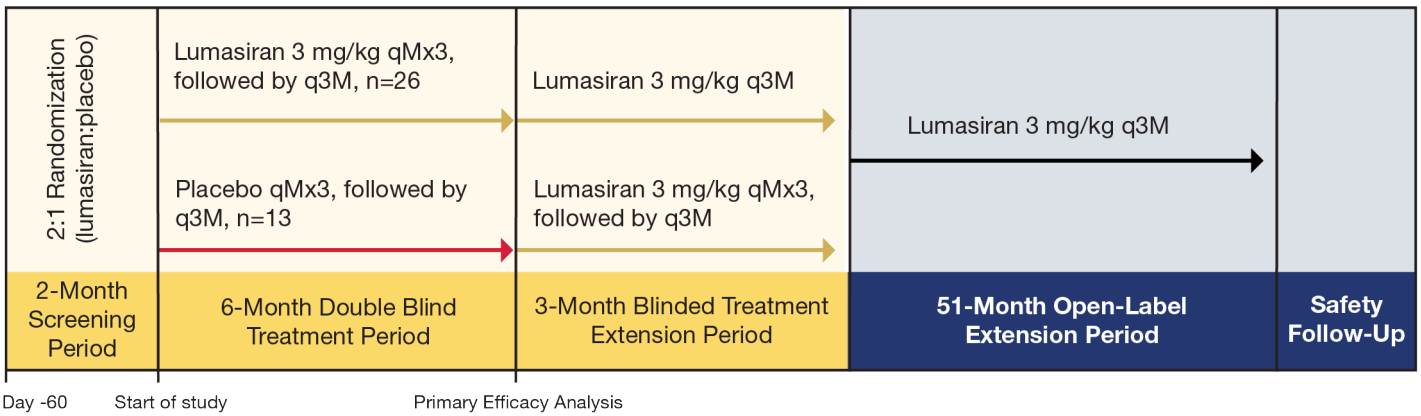
The Clinical Trials (ILLUMINATE-A and -B)

Two phase 3 clinical trials (ILLUMINATE-A and ILLUMINATE-B) provided the basis for FDA's approval of lumasiran. For detailed information on the approval of lumasiran, please refer to the Integrated Review.

ILLUMINATE-A Trial Design

ILLUMINATE-A was a randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of lumasiran in patients aged six years and older with genetically confirmed PH1 and preserved renal function (defined as an eGFR ≥30 mL/min/1.73 m^2). Thirty-nine participants were randomized 2:1 (26 to lumasiran and 13 to placebo) with balanced demographic and baseline characteristics across groups. Participants received either lumasiran (3 mg/kg subcutaneously) or placebo, administered monthly for three doses followed by quarterly maintenance dosing (**Figure 2**).

Figure 2: *Study design for ILLUMINATE-A*
Key: q3M = every 3 months; qMx3 = monthly for 3 months

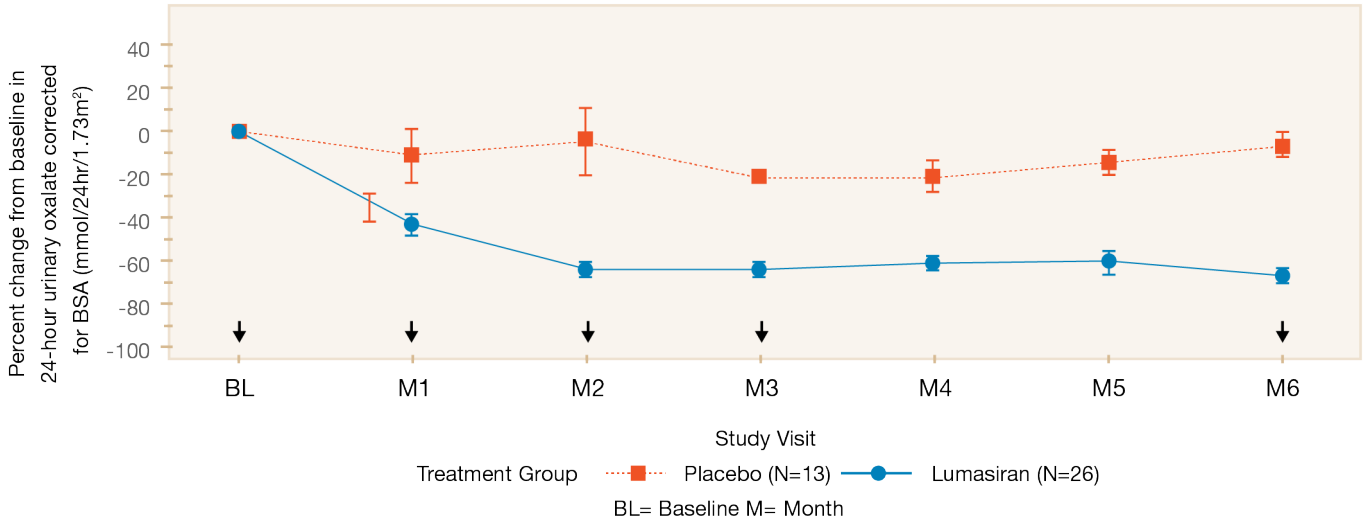


The primary efficacy endpoint was the percent change in 24-hour urinary oxalate excretion from baseline to Month 6, based on the average of Months 3 and 6. Secondary endpoints included the proportion of patients achieving urinary oxalate levels of ≤1.5 times the upper limit of normal.

ILLUMINATE-A Clinical Trial Results

Placebo-controlled data from ILLUMINATE-A provided evidence of a large treatment effect of lumasiran in patients with high baseline urinary oxalate levels ≥6 years of age with PH1 and relatively preserved kidney function, including normalization of urinary oxalate excretion in approximately half of participants. At Month 6, participants treated with lumasiran experienced a mean reduction of approximately 65% in 24-hour urinary oxalate, compared with a 12% reduction among those receiving placebo (**Figure 3**). The between-group difference for the primary endpoint was statistically significant. For the secondary endpoints, no placebo-treated participants achieved urinary oxalate levels within the normal range, while 52% of lumasiran-treated participants did (95% CI for between-group difference: 0.23-0.70; p=0.0011). Reductions were consistent across baseline subgroups, including those with high baseline urinary oxalate levels.

Figure 3: *ILLUMINATE-A Clinical Trial Results*

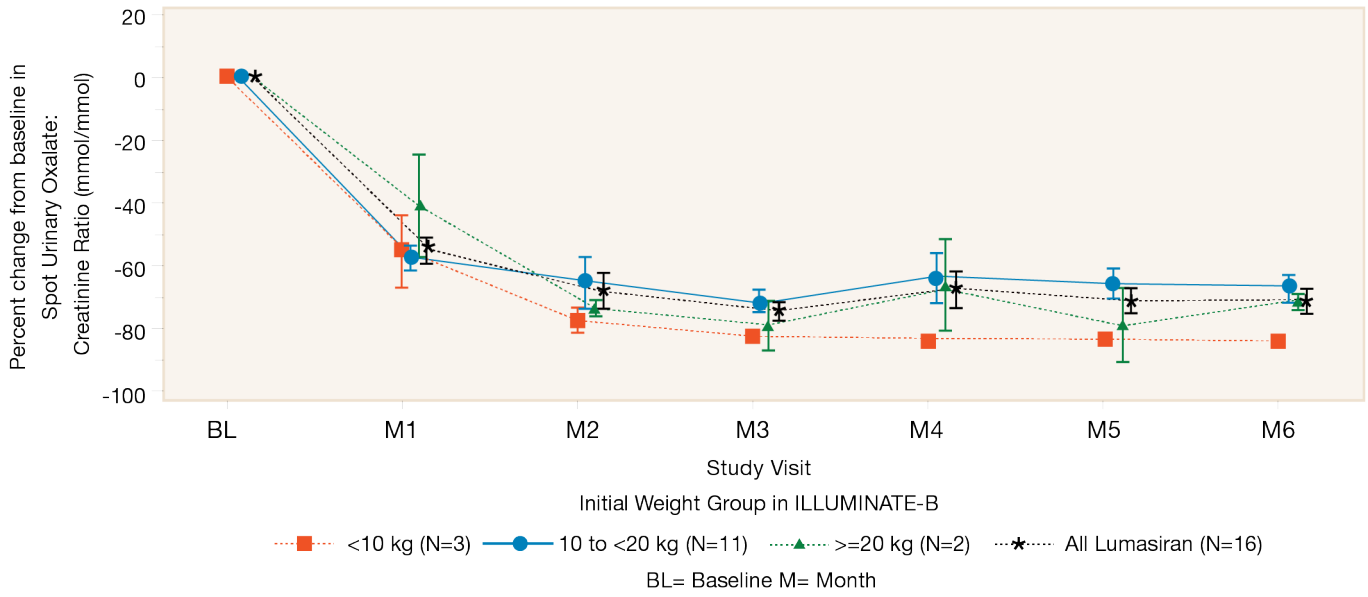


ILLUMINATE-B Trial Design

ILLUMINATE-B was an open-label, single-arm trial that enrolled 16 infants and young children (aged 3 months to 5 years) with PH1. All participants received weight-based lumasiran dosing, with monthly induction for three months for all patients, then monthly maintenance regimens for those under 10kg, and quarterly maintenance for those ≥10kg.

The primary endpoint for ILLUMINATE-B was the percent change in spot urinary oxalate-to-creatinine (Ox/Cr) ratio from baseline to Month 6. Although ILLUMINATE-B lacked a concurrent control, the Agency believed the results of the trial were likely to be interpretable, assuming the magnitude of reduction in urinary oxalate and time course were generally consistent with the findings in ILLUMINATE-A. Because it is difficult to obtain 24-hour urine collections in young children, first morning urinary Ox/Cr was used as the endpoint in ILLUMINATE-B. Urine Ox/Cr was shown to be comparable to 24-hour urinary oxalate normalized to body surface area (BSA) in patients >6 years of age with PH1; hence, urine Ox/Cr was used to compare the effects of lumasiran across age groups.

Figure 4: *ILLUMINATE-B Clinical Trial Results*



ILLUMINATE-B Clinical Trial Results

At Month 6, the mean percent reduction in urinary oxalate was approximately 72% (Figure 4). The data from ILLUMINATE-B provided evidence of a treatment effect in patients <6 years of age that was consistent with the treatment effect observed in ILLUMINATE-A and supported extension of the indication down to birth.

The magnitude of decrease from baseline in urine Ox/Cr in ILLUMINATE-B was consistent with the observed effect on 24-hour urine oxalate seen in ILLUMINATE-A, supporting FDA's conclusion of effectiveness in patients <6 years of age with PH1 and relatively preserved kidney function.

Conclusion

Although the manifestations of PH1 can be serious, calcium oxalate stones are slow to form and pass and loss of kidney function is generally gradual. As such, and given the rarity of the disease, it would be challenging to detect effects on clinical events within a trial of reasonable duration, given the time to observe clinically meaningful outcomes. Therefore, the development program was designed to assess treatment effects on urinary oxalate excretion.

Key Takeaways

- Evidence from natural history and registry data was critical in establishing the predictability of clinical outcomes by linking urinary oxalate levels to longer-term renal outcomes that could not be feasibly measured during a trial of reasonable duration, thereby supporting its use as a surrogate endpoint within the context of PH1.
- The observed changes in 24-hour urinary oxalate aligned with the biological mechanism of disease and were consistent with known relationships between oxalate burden and kidney outcomes.
- Biomarker-based surrogate endpoints can enable evaluation of therapeutic benefit in rare disease drug development programs when supported by robust scientific rationale and a strong evidentiary link to clinical outcomes. This approach provides a model for advancing drug development when clinical endpoints cannot be measured within a reasonable trial duration due to slower disease progression.
- The ILLUMINATE-A and ILLUMINATE-B clinical trials established a consistent and reproducible treatment effect on the surrogate endpoint across the evaluated PH1 disease population.

Support for the use of urinary oxalate as a surrogate for clinical outcomes in PH1 in patients with relatively preserved kidney function was based primarily on:

- Knowledge of the pathophysiology of the disease and the causal role of urinary oxalate in kidney stone formation, nephrocalcinosis, and loss of kidney function; along with
- Epidemiologic data (registries) showing an association between urinary oxalate and loss of kidney function, particularly in patients with high levels of urinary oxalate; and
- Observational data from patients treated with pyridoxine or liver transplant showing associations between reductions in urinary oxalate and preservation of kidney function.

This case study illustrates how, in rare disease drug development, a surrogate endpoint can be used to support approval when it is fit-for-purpose, and it also highlights how a biomarker can enable meaningful evaluation of treatment benefit when traditional clinical outcomes cannot be effectively measured within a trial's duration.

By drawing upon insights from natural history and registry data, the lumasiran development program provides an example of how surrogate endpoints can advance product evaluation and support regulatory decision-making in rare disease drug development.

Critical Thinking Questions for a Rare Disease Drug Development Program

Does the rare disease have a slowly progressive course? If so, have trial feasibility and duration been considered with the potential need for a surrogate endpoint that predicts clinical benefit?

When relying on natural history and registry data for identification of a biomarker-based surrogate endpoint, is there sufficient evidence to demonstrate that changes in the biomarker, and the magnitude of change, are reasonably likely to predict clinical benefit?

Has early engagement with FDA adequately addressed the proposed surrogate endpoint strategy? Were the plans to establish the biomarker's predictability of clinical outcomes discussed early in the development program?

Considerations when assessing whether a biomarker is appropriate as a surrogate endpoint in the development program:

- Is there a clear understanding of the pathophysiology and the natural history of the disease for which the product is intended to treat?
- Does the biomarker or do the biomarkers reflect the underlying disease pathophysiology?
- Is there evidence that the biomarker is on the causal pathway of disease?
- Is the biomarker or are the biomarkers supported by a clear mechanistic rationale?
- If applicable, are the bioanalytical assays used to measure the biomarkers validated?
- Are there epidemiological data from registries, natural history studies, or other sources that could be leveraged to inform the ability of the biomarker to predict clinical benefit?

We recommend meeting with the Agency early[7] in the drug development program to reach alignment regarding endpoint selection, trial design, and the approach to demonstrate substantial evidence of effectiveness.

[7] Please refer to the Additional Resources section for guidance on how to engage early with FDA, including information on Critical Path Innovation Meetings, INTERACT Meetings, and Pre-IND Meetings

Additional Resources

1. Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause https://www.fda.gov/media/191247/download
2. Guidance for Industry: Critical Path Innovation Meetings. https://www.fda.gov/media/89497/download
3. Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products. https://www.fda.gov/media/172311/download
4. Draft Guidance for Industry: Early Drug Development and the Role of Pre-IND Meetings. https://www.fda.gov/media/117322/download

Case Study References by Order of Appearance

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- See the LEADER 3D Case Study User Guide available at https://www.fda.gov/media/185425/download.
- See the FDA webpage with a list of guidance documents for Rare Disease Drug Development available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.
- See FDA Integrated Review document for Lumasiran (Oxlumo), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214103Orig1s000IntegratedR.pdf.

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- See National Institutes of Health's Primary hyperoxaluria, type 1 page for more information on the disease, available at https://rarediseases.info.nih.gov/diseases/2835/primary-hyperoxaluria-type-1.
- See NCATS Toolkit for Patient-Focused Therapy Development for more information on natural history studies, available at https://toolkit.ncats.nih.gov/module/discovery/starting-a-patient-registry-natural-history-study-database/natural-history-study/.
- See National Center for Biotechnology Information's BEST (Biomarkers, EndpointS, and other Tools) Resource for additional information on surrogate endpoints and their regulatory use, available at https://www.ncbi.nlm.nih.gov/books/NBK338448/.
- See FDA's Surrogate Endpoint Resources for Drug and Biologic Development for more information on surrogate endpoints and their regulatory use, available at https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development.

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- See draft guidance for industry Rare Diseases: Natural History Studies for Drug Development (March 2019), available at https://www.fda.gov/media/122425/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See the FDA website for up-to-date guidance documents for rare disease drug development available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.
- See draft guidance for industry Rare Diseases: Natural History Studies for Drug Development (March 2019), available at https://www.fda.gov/media/122425/download. When final, this guidance will represent the Agency's current thinking on this topic.

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- See guidance for industry Rare Diseases: Considerations for the Development of Drugs and Biological Products (December 2023), available at https://www.fda.gov/media/119757/download.
- See Milliner DS, McGregor TL, Thompson A, et al, 2022, End points for clinical trials in primary hyperoxaluria, CJASN, 15(7):1056-1065, available at https://doi.org/10.2215/CJN.13821119.
- See Hopp K, Cogal AG, Bergstralh EJ, et al, 2015, Phenotype-genotype correlations and estimated carrier frequencies of primary hyperoxaluria, J Am Soc Nephrol, 26(10):2559-2570, available at https://doi.org/10.1681/ASN.2014070698.

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- See draft guidance for industry Rare Diseases: Natural History Studies for Drug Development (March 2019), available at https://www.fda.gov/media/122425/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See FDA Integrated Review document for Lumasiran (Oxlumo), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/214103Orig1s000IntegratedR.pdf.

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- See draft guidance for industry Considerations for the use of the Plausible Mechanism Framework to Develop Individualized Therapies that Target Specific Genetic Conditions with Known Biological Cause (February 2026), available at https://www.fda.gov/media/191247/download. When final, this guidance will represent the Agency's current thinking on this topic.