Fosdenopterin (Nulibry)

Use of a Single Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence to Demonstrate Substantial Evidence of Effectiveness for a Rare Disease

Prior to reading this case study, please refer to the LEADER 3D Case Study User Guide as an informational resource. 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.

Introduction

This case study discusses the demonstration of substantial evidence of effectiveness for the U.S. Food and Drug Administration's (FDA) approval of fosdenopterin (Nulibry). For further details on this case study, please refer to the Integrated Review.

Fosdenopterin is a substrate replacement therapy for cyclic pyranopterin monophosphate (cPMP). It is used to treat molybdenum cofactor deficiency (MoCD) Type A—a rare, life-threatening, autosomal recessive disease. Most children with MoCD succumb to the disease within the first years of life (median survival at 36 months).

For all drugs approved in the U.S., Section 505(d) of the Federal Food, Drug and Cosmetic (FD&C) Act (21 U.S.C. § 355(d), states that a drug's effectiveness must be established by substantial evidence. The statute defines substantial evidence as "evidence consisting of adequate and well-controlled investigations, including clinical investigations by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof." Reflecting the importance of independent substantiation of experimental results, FDA generally requires two adequate and well-controlled investigations, each convincing on its own, to establish effectiveness.[1] However, the law also states, "If [FDA] determines, based on relevant science, that data from one adequate and well-controlled investigation and confirmatory evidence are sufficient to establish effectiveness, [FDA] may consider such data and evidence to constitute substantial evidence."[2] Although the topic of establishing safety is not discussed in this case study, please note that FDA approval is not solely based on demonstration of substantial evidence of effectiveness but also on a determination that a drug is safe for its intended use, among other things.

FDA Guidance Corner

Note: The FDA Guidance Corner includes excerpts of draft FDA guidance documents which, when final, will represent the Agency's current thinking on topics within the case study. For up-to-date guidance documents, please search Guidance Documents for Rare Disease Drug Development | FDA.

In this case study, the Applicant engaged with the FDA early in planning for their new drug application. Meeting with the FDA early in the drug development process is crucial so that potential issues may be addressed prior to pivotal clinical studies.

Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry* (September 2023)

When a meeting is needed, a written request must be submitted to the FDA via the electronic gateway, or to CDER via the CDER NextGen Portal, as applicable. Requests should be addressed to the appropriate center and review division or office, and if previously assigned, submitted to the relevant application (e.g., investigational new drug application [IND], new drug application [NDA], biologics license application [BLA]).

If necessary, noncommercial IND holders may also submit the meeting request via the appropriate center's document room.

[1] For further information regarding characteristics of adequate and well-controlled investigations, see 21 CFR 314.126.

[2] See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019).

In this case study, to demonstrate substantial evidence of effectiveness for fosdenopterin, the Applicant engaged with the Agency early in planning for their New Drug Application submission to discuss (1) the study design and analysis plan for their one adequate and well-controlled clinical investigation and (2) the types of confirmatory evidence that would be submitted to establish substantial evidence of effectiveness.

The single adequate and well-controlled clinical investigation is an analysis of data pooled from a cohort of 13 treated participants drawn from 2 clinical trials and a retrospective non-interventional (observational) study compared to an external control consisting of 18 genotype-matched untreated participants from a retrospective natural history study (NHS).

The two types of confirmatory evidence included (a) pharmacodynamic (PD) evidence and (b) evidence from a relevant animal model.

Introduction to the Rare Condition

MoCD Type A is a rare (1 in 200,000) and rapidly progressive, life-threatening disease with an autosomal recessive pattern of inheritance. MoCD typically presents acutely in the neonatal period or early infancy and is characterized by intractable seizures, metabolic acidosis, failure to thrive, feeding difficulties, and axial hypotonia with limb hypertonia. The estimated U.S. prevalence of MoCD Type A is 45 to 54 patients, all under 10 years of age.

Variants in the molybdenum cofactor synthesis 1 (MOCS1) gene lead to a deficiency of cyclic pyranopterin monophosphate (cPMP), which is necessary for the synthesis of molybdenum cofactor (**Figure 1.A**).

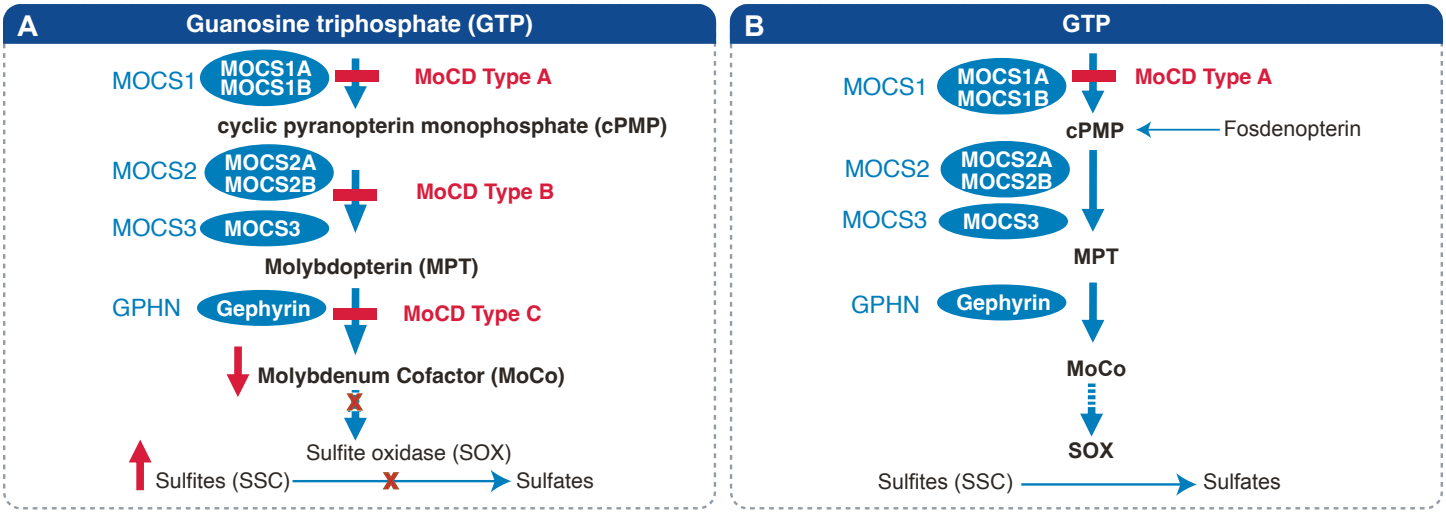
FDA Guidance Corner

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

Many rare diseases are serious conditions with no approved treatments, leaving substantial unmet medical needs for patients. FDA recognizes that rare diseases are highly diverse with varying prevalence, rates of progression, and degrees of heterogeneity that can affect both clinical manifestations and disease courses even within a condition.

Further complexity is added depending on what is known about a disease's natural history and pathophysiology. **As such, no one program can be designed exactly like another. FDA is committed to helping sponsors create successful drug development programs that address the challenges posed by each disease and encourages sponsors to engage early with the Agency to discuss their drug development program.**

Figure 1: (A) *Molybdenum cofactor (MoCo) biosynthetic pathway. MoCo is synthesized from Guanosine triphosphate (GTP). The schematic shows the enzymes (in blue circles) and their respective genes MOCS1, MOCS2, MOCS3, and GPHN that are involved in each step of the MoCo biosynthetic pathway. The three different types of diseases associated with MoCD (Types A, B, and C) and their respective genetic alterations (red boxes) are also indicated in the pathway.* ***(B)*** *MOA of fosdenopterin. Fosdenopterin replaces the deficient cPMP caused by variants in the MOCS1 gene (MoCD Type A), thereby restoring MoCo biosynthesis and SOX activity in converting toxic sulfites to sulfates.*



This cPMP deficiency ultimately compromises the catalytic activity of the molybdenum cofactor-dependent enzyme, sulfite oxidase (SOX), resulting in the accumulation of neurotoxic sulfites, primarily S-sulfocysteine (SSC). The resulting elevated levels of urinary sulfites including SSC are characteristic findings of MoCD. Such elevated toxins, when present in the central nervous system (CNS), lead to the largely irreversible neuronal injury observed in patients with this disease.[3]

Fosdenopterin Mechanism of Action

Fosdenopterin is a substrate replacement therapy that provides an exogenous source of cPMP, which is converted to molybdopterin (MPT). MPT is then converted to molybdenum cofactor (MoCo), which is needed for the activation of molybdenum-dependent enzymes, including SOX, an enzyme that reduces levels of neurotoxic sulfites (**Figure 1.B**).

The Single Adequate and Well-Controlled Investigation[4]

The efficacy of fosdenopterin was demonstrated in an adequate and well-controlled clinical investigation that used overall survival data pooled from a cohort of 13 genetically confirmed participants with MoCD Type A drawn from 2 clinical trials and a retrospective non-interventional (observational) study (MCD 201, MCD 202, and MCD 501) compared to an external control consisting of 18 genotype-matched untreated participants from a retrospective natural history study (NHS) (Study MCD-502) (**Figure 2, top panel 2**). The mean survival time at up to 3 years of follow-up was 32 months for fosdenopterin-treated participants and 24 months for the untreated genotype-matched historical control group.

At 3 years, the Kaplan-Meier survival probability was 84% (95% confidence interval [CI] (49, 96)) for fosdenopterin-treated participants and 55% (30, 74) for genotype-matched historical control group, as seen in **Figure 3**.

This approach, which incorporated the use of a retrospective NHS as an external control, produced interpretable results for reasons including the following:

1. Interaction between the review division and Applicant to:
   - Determine comparability between the treated and genotype-matched control groups, and;
   - Develop a statistical analysis plan (SAP) that controlled for potential confounders and ensured data quality.
2. Use of a reliable and objective endpoint (i.e., mortality)
3. A large treatment effect size
4. Robustness of the data to various sensitivity analyses and assumptions[5]

Key Terminology: Endpoints and Endpoint Considerations

An endpoint is a precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question.

A precise definition of an endpoint typically specifies:

- The type of assessments made;
- The timing of those assessments;
- The assessment tools used; and
- Possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.

Sponsors developing novel clinical outcome assessments should identify their assessments' characteristics early in their drug development program; late identification of these characteristics may delay drug development.

FDA Guidance Corner

In this case study, substantial evidence of effectiveness is demonstrated using one adequate and well-controlled clinical investigation plus confirmatory evidence.

For different approaches to establish substantial evidence of effectiveness, please refer to the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) which, when final, will represent the Agency's current thinking on the topic.

[3] Atwal, PS and F Scaglia, 2016, Molybdenum Cofactor Deficiency Mol Genet Metab, 117(1):1-4.

[4] For more information about the trial design (e.g., inclusion and exclusion criteria), please refer to the Integrated Review, on page 25.

[5] To learn more about the robustness of the sensitivity analysis, please refer to the Integrated Review, on page 38.

Figure 2: (Top panel) *Schematic depicting the design for the single adequate and well-controlled investigation that used overall survival data pooled from a cohort of 13 genetically confirmed participants with MoCD Type A drawn from two clinical trials and a retrospective non-interventional (observational) study (MCD 201, MCD 202, and MCD 501) compared to an external control consisting of 18 genotype-matched untreated participants from a retrospective natural history study (NHS) (Study MCD-502).* ***(Bottom panel)*** *Confirmatory evidence (data from relevant animal models and PD studies) that supported fosdenopterin's application for substantial evidence of effectiveness.*

Substantial Evidence of Effectiveness
Single Adequate and Well-Controlled Investigation

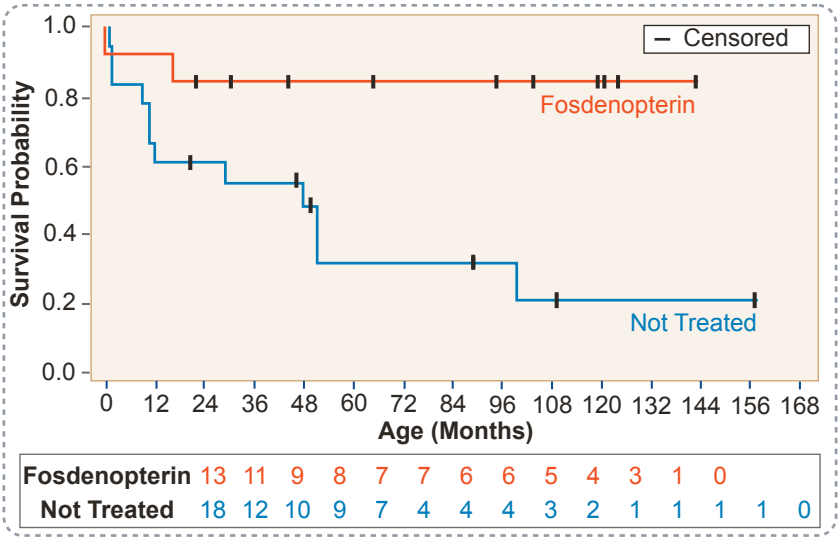
Data from Clinical and Observational Studies Treated Participants	Genotype-Matched Untreated Participants
n = 13 Patients were treated with recombinant form of the **fosdenopterin** **Clinical Studies** MCD-201 MCD-202 **Retrospective Observational Study** MCD-501	n = 18 **Retrospective Observational NHS External Control** MCD-502

Efficacy was assessed by comparing the overall survival of the 13 patients treated with fosdenopterin against 18 genotyped-matched patients with MoCD Type A

AND...Confirmatory Evidence

Evidence from a Relevant Animal Model	Mechanistic or Pharmacodynamic Evidence
• Elevated plasma and urinary SSC levels are biochemical hallmarks of the disease. • Animal data using a mouse model of MoCD Type A demonstrated a reduction of plasma and brain SSC levels. • There is currently no evidence suggesting that a species difference between animals and humans would alter the permeability or transport of fosdenopterin across the blood brain barrier. • The data demonstrated improved survival in the mouse model of the disease.	• Higher plasma fosdenopterin exposures were generally associated with lower urine SSC.

Figure 3: *Kaplan-Meier survival probability for fosdenopterin-treated (red) and untreated (blue) participants.*[6]



FDA Guidance Corner

"The quality and strength of mechanistic data exist on a spectrum, ranging from exploratory in nature to results that demonstrate clear evidence for a particular pathophysiological mechanism of disease and the drug's effect on the established mechanism."

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023). When final, this guidance will represent the Agency's current thinking.

[6] Figure 3 was adapted from Farrell, S, J Karp, R Hager, Y Wang, O Adeniyi, J Wang, L Li, L Ma, J Peretz, M Summan, N Kong, M White, M Pacanowski, D Price, J Filie, K Donohue, and H Joffe, 2021, Regulatory news: Nulibry (fosdenopterin) approved to reduce the risk of mortality in patients with molybdenum cofactor deficiency type A: FDA approval summary. J Inherit Metab Dis., 44(5):1085-1087.

Highlights

- The challenge associated with an extremely limited patient population was overcome by combining data from more than one clinical investigation.
- The use of NHS data as an external control was acceptable because of the comparability between treated participants and the genotype-matched untreated participants in the external control.
- The survival endpoint used to support substantial evidence of effectiveness was reliable and objective and therefore fit for regulatory use.
- A large treatment effect was observed between the control and treatment groups.

When final, these guidance documents will represent the Agency's current thinking on these topics:

- Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)
- Draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019)

The Confirmatory Evidence

In this case study, the Applicant submitted two types of confirmatory evidence to demonstrate substantial evidence of effectiveness, including:

- PD effect on reduction of urinary SSC in patients with MoCD Type A.
- Data from a knockout mouse model of MoCD Type A to support a PD relationship between fosdenopterin administration and reduction of plasma and brain SSC, and improved survival.[7]

Mechanistic or Pharmacodynamic Evidence

Mutations in the MOCS1 gene, which cause MoCD Type A, result in the accumulation of systemic SSC (a toxic sulfite) (**Figure 1**), and elevated SSC concentrations can be detected in urine.

Treatment with fosdenopterin reduced urinary SSC concentrations in patients with MoCD Type A, and this reduction was sustained over 48 months. Importantly, higher exposures to fosdenopterin were associated with lower concentrations of SSC in the urine.

Urinary SSC represents a PD response biomarker because SSC is linked to the canonical pathophysiologic pathway for MoCD Type A, urinary SSC can be measured using a validated bioanalytical method, and urinary SSC exhibits an exposure-response relationship with fosdenopterin.

FDA Guidance Corner

In this case study, natural history study data was leveraged as an external control. Natural history studies can play an important role at every stage of drug development. When final, this guidance will represent the Agency's current thinking on the use of natural history studies for rare diseases:

Draft guidance for industry *Rare Diseases: Natural History Studies for Drug Development* (March 2019)

Natural History Studies: 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 onset and progression to major morbidity or mortality. 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.

External Controls: In an externally controlled trial, outcomes in participants receiving the test treatment according to a protocol are compared to outcomes in a group of people external to the trial who had not received the same treatment.

In this case study, the Applicant uses data collected from an adequate control group to discriminate patient outcomes caused by the investigational drug from outcomes caused by other factors (i.e., what would have happened if similar patients had not received the investigational drug). FDA regulations recognize historical controls as a possible control group (usually reserved for special circumstances); however, inability to control for certain biases could limit the ability of externally controlled trials to demonstrate substantial evidence of effectiveness. Bias may be mitigated in certain situations where the disease course is predictable and the treatment effect dramatic.

For additional information regarding adequate external controls, please refer to the draft guidance for industry Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products (February 2023) which, when final, will represent the Agency's current thinking.

[7] See Section 6.1.5 and Section 13 in the Integrated Review, for more information on the human study (pg. 23) and animal study (pg. 62), respectively.

Evidence from a Relevant Animal Model[8]

Data from a mouse model of MoCD Type A (MOCS1 knockout mice) demonstrated a reduction of plasma and brain SSC levels and substantial improvement in survival when treated with fosdenopterin compared to placebo-treated mice. In addition, tissue distribution studies in the rat following intravenous radiolabeled fosdenopterin demonstrated the presence of fosdenopterin in the non-circumventricular CNS (**Figure 2, bottom panel**). These data were supportive of the observations in the clinical pharmacology studies.

Although species differences exist for the transport of drugs to the brain, there is currently no evidence suggesting that a species difference between animals and humans would alter the permeability or transport of fosdenopterin across the blood brain barrier.

FDA Guidance Corner

In this case study, substantial evidence of effectiveness is demonstrated using one adequate and well-controlled clinical investigation plus confirmatory evidence. In this guidance which, when final, will represent the Agency's current thinking, different types of confirmatory evidence are discussed:

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

Confirmatory Evidence: The quantity (e.g., number of sources) of confirmatory evidence necessary to support effectiveness may vary across development programs. Importantly, the quantity of confirmatory evidence needed in a development program will be impacted by the features of, and results from, the single adequate and well-controlled clinical investigation that the confirmatory evidence is intended to substantiate. It may be possible for a highly persuasive adequate and well-controlled clinical investigation to be supported by a lesser quantity of confirmatory evidence, whereas a less-persuasive adequate and well-controlled clinical investigation may require a greater quantity of compelling confirmatory evidence to allow for a conclusion of substantial evidence of effectiveness.

Mechanistic or Pharmacodynamic Evidence: Under certain circumstances, strong mechanistic evidence of the drug's treatment effect in a particular disease may be appropriate to use as confirmatory evidence. In such cases, (1) the pathophysiology of the disease should be well understood and (2) the drug's mechanism of action should be both clearly understood and shown to directly target the major drivers of the pathophysiology.

Evidence from a Relevant Animal Model: Animal data (e.g., proof-of-concept data, pharmacological studies, toxicology studies) are used in drug development for a number of purposes, including to help characterize potential pharmacodynamic effects (which may be done either in healthy animals or in animal models of disease); provide evidence of activity in an animal model of disease, using an endpoint that is intended to reflect or translate to a similar outcome in humans with disease; or profile drug toxicity.

Typically, results of studies conducted in an animal model of disease are intended to support progressing a drug candidate forward from preclinical to clinical development, rather than to support a finding of substantial evidence. Infrequently, however, sponsors can use data from an established animal model of disease as confirmatory evidence of effectiveness; in such cases, sponsors should discuss in advance these planned nonclinical studies with the appropriate FDA review division.

For more information on bioanalytical method validation, please see the guidance for industry *Bioanalytical Method Validation* (May 2018). For questions about the relevance of an animal model, please consult the FDA

[8] For more information on the animal model data (e.g., toxicology data), please refer to the Integrated Review on page 62.

Conclusion

For approval of a marketing application, the FDA requires establishing substantial evidence of effectiveness for the drug, among other requirements.

The effectiveness of fosdenopterin for treating MoCD Type A was established based on the survival benefit observed in one adequate and well-controlled clinical investigation and was supported by additional confirmatory evidence. The confirmatory evidence came from:

1. Extensive, longitudinal sampling of urinary SSC, a human PD biomarker and;
2. Supportive PD data from a knockout animal model of MoCD showing improved survival and a reduction of plasma and brain SSC levels when treated with fosdenopterin (**Figure 2**).

Despite the limited number of study participants, the Applicant was able to meet FDA's standard for substantial evidence of effectiveness for fosdenopterin in the treatment of MoCD Type A using data from one adequate and well-controlled investigation and confirmatory evidence.

Critical Thinking Questions for a Rare Disease Drug Development Program

Will the Development Plan Establish Substantial Evidence of Effectiveness?

Rare disease drug developers should discuss the rationale for their proposed approach to demonstrate substantial evidence of effectiveness with FDA early in the development of their therapy. When planning for and designing a clinical investigation(s) for a rare disease medical product, we encourage consideration of the following questions:

1. **What is the development plan to demonstrate substantial evidence of effectiveness?**
   - If the plan does not include two adequate and well-controlled clinical investigations, what is the scientific justification for the proposed development approach?
2. **When planning to use a one adequate and well-controlled clinical investigation plus confirmatory evidence approach, consider the following questions:**
   - What is the plan for designing an adequate and well-controlled investigation?
   - Is a clinically meaningful endpoint(s) being measured? How reliable and objective is the endpoint(s)?
   - Will a biomarker be utilized?
   - What type of control group is being considered in the clinical investigation?
   - What is the anticipated treatment effect of the medical product?

Please note that the quantity of confirmatory evidence may be impacted by the design and results of the one adequate and well-controlled clinical investigation.

3. **What is the description of the confirmatory evidence? (Prior to initiating clinical investigations, consider the following questions that pertain to confirmatory evidence):**
   - Is there an available animal model for the rare disease?
   - Is there a biomarker in animals that reliably predicts response to treatment in humans?
   - Are the methods of analysis analytically validated?

We recommend speaking to the Agency to reach alignment regarding the design of the one adequate and well-controlled clinical investigation and related confirmatory evidence.

Key Takeaways

- There are circumstances when it might be appropriate for sponsors to use data from an established animal model or pharmacodynamic/mechanistic data as confirmatory evidence to support substantial evidence of effectiveness.
- If contemplating using confirmatory evidence to support an FDA application, please talk with the FDA early in the drug development process. For information on how to interact with the FDA, please read the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023).
- For recommendations regarding confirmatory evidence, read the draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023).

When final, these guidance documents will represent the Agency's current thinking.

Case Study References by Order of Appearance

Page 1

- See the LEADER 3D Case Study User Guide available at https://www.fda.gov/media/185425/download.
- See FDA Integrated Review document for fosdenopterin (Nulibry) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214018Orig1s000IntegratedR.pdf.
- See the FDA Guidance Documents for Rare Disease Drug Development webpage available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.
- See draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry* (September 2023) available at https://www.fda.gov/media/172311/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See 21 CFR 314.126 for more information on the characteristics of adequate and well-controlled investigations available at https://www.govinfo.gov/content/pkg/CFR-2010-title21-vol5/pdf/CFR-2010-title21-vol5-sec314-126.pdf.
- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) available at https://www.fda.gov/media/133660/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) for important considerations in rare disease drug and biologics development, available at https://www.fda.gov/media/119757/download.

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- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019) available at https://www.fda.gov/media/133660/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See Atwal, PS and F Scaglia, 2016, Molybdenum Cofactor Deficiency Mol Genet Metab, 117(1):1-4 available at https://pubmed.ncbi.nlm.nih.gov/26653176/.
- See page 25 of the FDA Integrated Review document for more information about the trial design including inclusion and exclusion criteria for fosdenopterin (Nulibry) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214018Orig1s000IntegratedR.pdf.
- See page 38 of the FDA Integrated Review document for more information about the robustness of the sensitivity analysis for fosdenopterin (Nulibry) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214018Orig1s000IntegratedR.pdf.

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- See draft guidance for industry Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (September 2023) available at https://www.fda.gov/media/172166/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See Farrell, S, J Karp, R Hager, Y Wang, O Adeniyi, J Wang, L Li, L Ma, J Peretz, M Summan, N Kong, M White, M Pacanowski, D Price, J Filie, K Donohue, and H Joffe, 2021, Regulatory news: Nulibry (fosdenopterin) approved to reduce the risk of mortality in patients with molybdenum cofactor deficiency type A: FDA approval summary. J Inherit Metab Dis., 44(5):1085-1087 available at https://pubmed.ncbi.nlm.nih.gov/34337775/.

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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 draft guidance for industry *Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products* (February 2023) available at https://www.fda.gov/media/164960/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023) available at https://www.fda.gov/media/172166/download. When final, this guidance will represent the Agency's current thinking on this topic.
- 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 Section 6.1.5 and Section 13 in the FDA Integrated Review for more information on the human study (pg. 23) and animal study (pg. 62) for fosdenopterin (Nulibry) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214018Orig1s000IntegratedR.pdf.

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- See draft guidance for industry Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence (September 2023) available at https://www.fda.gov/media/172166/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See guidance for industry *Bioanalytical Method Validation* (May 2018) available at https://www.fda.gov/media/70858/download.
- See page 62 of the FDA Integrated Review document for more information on the animal data (e.g., toxicology data) for fosdenopterin (Nulibry) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/214018Orig1s000IntegratedR.pdf.

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- See draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023) available at https://www.fda.gov/media/172311/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness with One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023) available at https://www.fda.gov/media/172166/download. When final, this guidance will represent the Agency's current thinking on this topic.