Odevixibat (Bylvay)

Developing Novel Clinical Outcome Assessment Instruments for Use in the Demonstration of 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 examines the development and use of clinical outcome assessments (COAs) in the new drug application for odevixibat (Bylvay), which was approved by the U.S. Food and Drug Administration (FDA) in 2021 for the treatment of pruritus in progressive familial intrahepatic cholestasis (PFIC). For further details on this case study, please refer to the Integrated Review.

Odevixibat is a reversible inhibitor of an ileal bile acid transporter (IBAT) that blocks the intestinal reabsorption of bile acids. It is used for treatment of pruritus (i.e., itching) in patients with PFIC.[1] PFIC is a rare condition that causes progressive liver disease, often leading to liver failure. Pruritus is a debilitating symptom in children with PFIC.

In this case study, the Applicant engaged with FDA early, and throughout their drug development program to develop and leverage novel COAs to evaluate pruritus in patients with PFIC.

Introduction to the Rare Disease

PFIC is a rare (incidence of 1 in 50,000 to 1 in 100,000) autosomal recessive condition with an estimated 400-500 patients in the United States. The disease presents during early childhood with signs and symptoms related to cholestasis (i.e., the buildup of bile acids in the liver), such as pruritus, jaundice, and growth failure. The disease can progress to cirrhosis leading to liver failure, and patients with PFIC are at risk of developing hepatocellular carcinoma.

Pruritus, a hallmark clinical symptom of this disease, can be severe and disruptive for patients and their families, and limits patients' ability to participate in daily activities. The physical manifestations include scratch marks, excoriations, and scarring due to persistent and unrelenting pruritus.

[1] Odevixibat may not be effective in PFIC type 2 patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3). For more information, please see the Prescribing Information.

FDA Guidance Corner

Note: The FDA Guidance Corner includes excerpts of FDA guidance documents, which, when final, 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, the Applicant engaged with the FDA early in the planning for their drug development program. Meeting with the FDA early in the drug development process is crucial so that potential issues may be addressed prior to conducting pivotal clinical studies.

This draft guidance describes the types of meetings available to sponsors:

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

When a meeting is needed, a written request must be submitted to the FDA via the electronic gateway or, in CDER, via the CDER NextGen Portal, as appropriate… Requests should be addressed to the appropriate Center and review division or office and, if previously assigned, submitted to the application (e.g., investigational new drug application (IND), new drug application (NDA), biologics license application (BLA), pre-application tracking system (PTS) Number (CBER)).

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

Current Treatment and Mechanism of Action

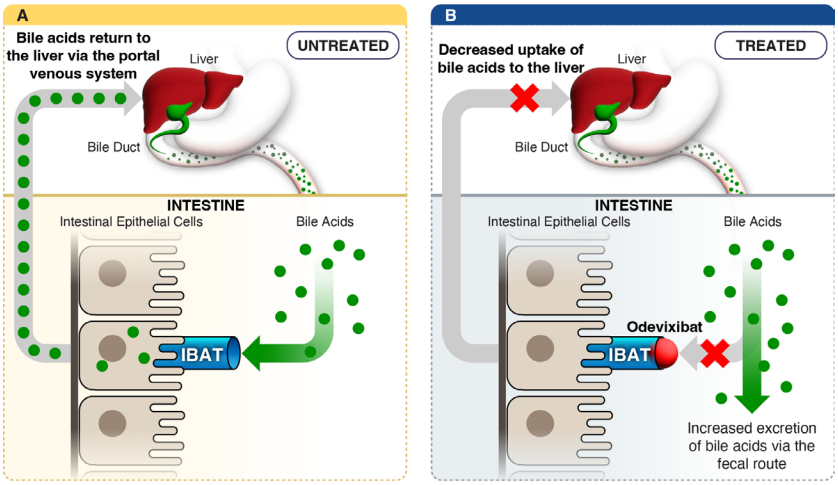
In patients with PFIC, the genes encoding the bile acid membrane transporters are mutated, resulting in impaired bile acid secretion by hepatocytes (i.e., liver cells).

This impaired secretion leads to a buildup of bile acids in the liver and results in symptoms of cholestasis, including pruritus. Before FDA's approval of odevixibat, there were no approved therapies for the treatment of pruritus in patients with PFIC.

Although some treatments are used off label in medical practice for pruritus, including the use of ursodeoxycholic acid, cholestyramine, antihistamines, naltrexone, rifampin, and ondansetron, most of these therapies do not ameliorate pruritus and have undesirable side effects. When the pruritus is severe and quality of life is significantly impacted, and pruritus does not respond to any available off-label treatments, two surgical options are available: biliary diversion (internal or external), or liver transplantation. Both surgical options are invasive and associated with serious complications, and lifelong immunosuppression is needed after liver transplantation. Therefore, before the approval of odevixibat, there was a high unmet medical need for treatment of pruritus in patients with PFIC.

Although the exact mechanism by which odevixibat improves pruritus in PFIC patients is not fully understood, it likely involves the inhibition of the IBAT (**Figure 1**). This inhibition blocks the intestinal reabsorption of bile acids, leading to their excretion and the reduction of accumulated bile acids in the liver. Consequently, this process may alleviate pruritus associated with PFIC.

Figure 1: *Mechanism of action of odevixibat.* ***(A)*** *In PFIC, bile acids (green circles) in the intestine (ileum) are reabsorbed at the apical surface of epithelial cells via the IBAT (blue cylinder) and returned to the liver via the portal venous system where they accumulate.* ***(B)*** *Odevixibat, an IBAT inhibitor (red circle) blocks the reuptake of bile acids, thereby decreasing hepatic accumulation of bile acids and increasing their excretion.*



FDA Guidance Corner

This guidance highlights important considerations in rare disease drug and biologics development:

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 need 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 particular challenges posed by each disease and encourages sponsors to engage early with the Agency to discuss their drug development program.

Key Terminology:

Observer-Reported Outcome (ObsRO) and Patient-Reported Outcome (PRO)

An **ObsRO** is a measurement based on a report of observable signs, events or behaviors related to a patient's health condition by someone other than the patient or a health professional.

Generally, ObsROs are reported by a parent, caregiver, or someone who observes the patient in daily life and are particularly useful for patients who cannot report for themselves (e.g., infants or individuals who are cognitively impaired).

A **PRO** is a measurement based on a report that comes directly from the patient (i.e., study participant) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else.

For more definitions, please refer to the NIH/FDA's BEST (Biomarkers, EndpointS, and other Tools) Resource.

The Clinical Outcome Assessments (COA)

Description of the COAs

A COA is a measure that describes or reflects how a patient feels, functions, or survives. There are four types of COAs: clinician-reported outcome (ClinRO) measures, observer-reported outcome (ObsRO) measures, patient-reported outcome (PRO) measures, and performance outcome (PerfO) measures. Given the participants' young age, this case study describes how the Applicant developed two novel COAs — consisting of an ObsRO measure and a PRO measure — to demonstrate the efficacy of odevixibat. The concepts of interest for the COAs were scratch (as assessed by the ObsRO) and itch (as assessed by the PRO).

The assessments on both the ObsRO and PRO measures were taken twice daily (once in the morning [AM] and once in the evening [PM]), and scores were recorded in an electronic diary. Both the ObsROs and PROs assessed the severity of pruritus on a 5-point ordinal scale in an electronic diary (**Table 1**). The ObsROs measured scratching severity (i.e., an indicator of a patient's level of itching) as observed by the caregivers, while the PROs measured itching intensity as directly reported by patients in electronic diaries. Due to the young ages of participants, the PRO measures were only administered to participants aged 8 to 18 years, while caregivers completed the ObsRO assessments for all enrolled participants.

Table 1: *COAs Included in the Clinical Trial.*

	Pruritus measure item (ObsRO)	Pruritus measure item (PRO)
Concept	Scratch	Itch
Endpoint Position	Primary	Secondary
Assessment Frequency	Twice daily (AM and PM)	Twice daily (AM and PM)
Ordinal Scale	0 = No scratching 1 = A little scratching 2 = Medium scratching 3 = A lot of scratching 4 = Worst possible scratching	0 = No itching 1 = A little itching 2 = Medium itching 3 = A lot of itching 4 = The worst itching

The COAs Conceptual Framework

The ObsRO Measure of Scratching Severity

The ObsRO is a single item assessment tool designed to measure scratching severity on a 5-point numeric rating scale ranging from 0 ("no scratching") to 4 ("the worst possible scratching"). The recall period is over the previous half day (i.e., since he/she went to bed last night, since he/she woke up this morning) (**Table 2**).

FDA Guidance Corner

This draft guidance highlights important considerations in COA development which, when final, will represent the Agency's current thinking:

Draft guidance for industry, FDA Staff, and other stakeholders *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessment* (June 2022)

A COA is a measure that describes or reflects how a patient feels, functions, or survives... There are four types of COAs: clinician-reported outcome (ClinRO), observer-reported outcome (ObsRO), patient-reported outcome (PRO), and performance outcome (PerfO). A COA is considered fit-for-purpose for the context of use when "level of validation associated with a medical product development tool is sufficient to support its context of use".[2]

Whether a COA is fit-for-purpose is determined by the strength of the evidence in support of interpreting the COA scores as reflecting the concept of interest within the context of use.

Decisions about whether a COA is fit-for-purpose are based on two considerations:

- The concept and context of use are clearly described.
- There is sufficient evidence to support a clear rationale for the proposed interpretation and use of the COA.

Key Terminology: "Concept of Interest" and "Context of Use"

- In a regulatory context, **the concept** (also referred to as **concept of interest**) is the aspect of an individual's clinical, biological, physical, or functional state, or experience that the assessment is intended to capture.
- **Context of use** is a statement that fully and clearly describes the way the medical product development tool is to be used and the regulated product development and review-related purpose of the use.

More definitions may be found in FDA's Patient-Focused Drug Development Glossary and NIH/FDA's BEST (Biomarkers, EndpointS, and other Tools) Resource.

[2] BEST (Biomarkers, EndpointS, and other Tools) Resource

The PRO Measure of Itching Severity

The PRO is a single item assessment tool designed to measure itch intensity on a 5-point numeric rating scale ranging from 0 ("no itching") to 4 ("the worst itching"). The recall period is over the previous half day (i.e., since you went to bed last night, since you woke up this morning) (Table 2).

Table 2: *Conceptual Frameworks of ObsRO and PRO Pruritus Items.*

Conceptual Framework of ObsRO Pruritus Item		
General Concept	**Item**	**Domain**
Daily Scratching	How bad was your child's worst scratching since he/she went to bed last night?	Nighttime Scratching
	How bad was your child's worst scratching since he/she woke up this morning?	Daytime Scratching
Conceptual Framework of PRO Pruritus Item		
General Concept	**Item**	**Domain**
Daily Itching	How bad was your worst itching since you went to bed last night?	Nighttime Itching
	How bad was your worst itching since you woke up this morning?	Daytime Itching

COAs Validity

To support the **validity** of the COAs, that is, the degree to which the evidence supports the interpretation and use of the pruritus scores in the trial, the Applicant conducted a targeted literature review, collected input from clinicians with PFIC expertise, conducted patient and caregiver interviews, and conducted quantitative analyses.

The outcome of these activities confirmed that pruritus was the most common and relevant symptom in patients with PFIC. Additionally, in patient listening sessions organized by FDA, families and caregivers of patients with PFIC confirmed that pruritus is a disabling symptom and can be severe and unrelenting, adversely affecting the quality of life of both children and their caregivers. Therefore, FDA agreed that pruritus was the most frequent and important symptom to assess for improvement in patients and the single-item ObsRO and PRO were reasonable tools to assess the severity of pruritus in these patients.

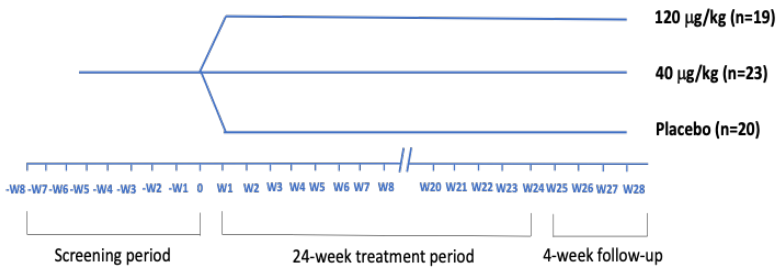
The Single Adequate and Well-Controlled Investigation (A4250-005)

Trial Design[3]

The Applicant used the ObsRO measures of pruritus to assess the efficacy of odevixibat by conducting one multicenter, adequate and well-controlled clinical investigation, Trial A4250-005 (NCT03566238).

The trial enrolled 62 participants between the ages of 6 months to 18 years in a randomized double-blind, placebo-controlled study as follows: placebo arm n=20; odevixibat 40 mcg/kg arm n=23; and odevixibat 120 mcg/kg arm n=19. The trial consisted of a 35-to-56-day screening period, a 24-week treatment period, and a 4-week follow-up period (Figure 2).

Figure 2: *Clinical Trial Study Design. Figure 2 was generated using information provided on page 27 of the Integrated Review for odevixibat (Bylvay), NDA 215498.*



[3] For more information on trial design (e.g., inclusion/exclusion criteria), please refer to page 31 of the Integrated Review.

Throughout the trial period, the ObsRO and PRO were used to measure the severity of participants' pruritus (i.e., scratching severity and itching intensity in participants ages 8-18 years, respectively) to compute the efficacy endpoints.

Trial Efficacy Endpoints

Primary Efficacy Endpoints

The Applicant's pre-specified primary efficacy endpoint was the mean percentage of assessments over the 24-week treatment period that are ≤ 1 (little or no scratching) or a 1-point drop from baseline. This "1-point drop from baseline" criterion involved comparing scratching scores collected with the ObsRO each day to a baseline average that is calculated from the scores collected over 14 days. FDA had two specific concerns regarding the Applicant's pre-specified primary efficacy endpoint:

1. There was uncertainty in the clinical meaningfulness of a 1-point drop in pruritus on a 0-4 scale.
2. There was uncertainty in the interpretability of comparing scores aggregated over different time intervals and considered scratching severity on a given day as a different clinical outcome than the average scratching severity experienced over the course of 14 days.

To address these concerns, FDA used an alternative endpoint for the primary assessment of efficacy, defined as the mean percentage of assessments over the 24-week treatment period that are ≤1 (no scratching or a little scratching). Thus, FDA did not include the 1-point drop from baseline criterion. To address the second concern regarding the interpretability of comparisons made between scores aggregated over different time intervals, FDA conducted analyses using "worst scratching severity" within a day and aggregate Daily Scratching Scores within at least a week (**Table 3**).

Table 3: *The Primary Efficacy Endpoints and Endpoint for Additional Evidence.*

Applicant-Specified Primary Efficacy Endpoint	• Mean percentage of assessments over the 24-week treatment period that are ≤ 1 or at least a 1-point drop from baseline.
FDA Alternative Primary Efficacy Endpoint	• Mean percentage of assessments over the 24-week treatment period that are ≤1 (no scratching or a little scratching), not including the 1-point drop from baseline criterion. • FDA considered this alternative primary efficacy analysis more readily interpretable with regard to clinical benefit.
FDA Alternative Endpoint for Additional Evidence of Within-Person Change in Pruritus	• Change in Worst Weekly Scratching Score from baseline (i.e., 28 days prior to the first dose) to the end-of-treatment (Weeks 21-24). • The FDA considered this endpoint as additional evidence for the mean percentage described.

Patient Reported Outcome Assessment (PRO)

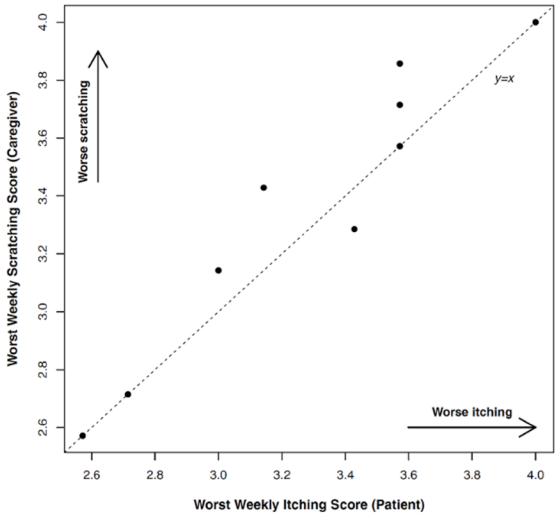
Few participants were able to self-report itching on the PRO instrument due to the young age of the participants (i.e., a total of nine participants with two in the placebo arm, two in the odevixibat 40 mcg/kg/day arm, and five in the odevixibat 120 mcg/kg/day arm). Given the limited sample size (n=9), formal statistical analyses were not conducted.

Comparability of Patient and Caregiver Pruritus Assessments

Additional evidence of treatment benefit was provided by evaluating differences between trial arms in change from baseline in Worst Weekly Scratching Score. There was general alignment between patient-reported itching severity and caregiver-reported scratching severity (Figure 3), although some uncertainty surrounds these findings due to the very small number of participants (n=9) with both PRO and ObsRO score data available during Study Days [-28, -1].

Note that all nine of these participants were aged 8 to 18 years as the PRO measures were only administered to participants aged 8 to 18 years while caregivers completed the ObsRO assessments for all enrolled participants. Although the PRO data did not contribute to the efficacy assessment, the results of the PRO supported the use of the ObsRO scratching scores to evaluate treatment effects.

Figure 3: Scatterplot of Worst Weekly Scratching Score (Representing Caregiver Perspective) by Worst Weekly Itching Score (Representing Patient Perspective) at Baseline (Study Days [-28, -1]) for Nine Participants for Whom Both Scores Were Available, Trial A4250-005. Figure 3 can be found on page 41 (Figure 3) of the Integrated Review for odevixibat (Bylvay), NDA 215498.



Trial Results

Substantial Evidence of Effectiveness: The One Adequate and Well-Controlled Clinical Investigation

The trial demonstrated a clinical benefit of odevixibat in the treatment of pruritus in participants with PFIC. The single randomized, double-blind, placebo-controlled phase 3 trial contributed to demonstration of substantial evidence of effectiveness for the following reasons:

1. **Statistically persuasive findings:** Participants with PFIC demonstrated clear improvement in pruritus scores after receiving odevixibat. Based on the Applicant's prespecified primary efficacy endpoint (see Primary Efficacy Endpoints section above), both the 40 mcg/kg/day and 120 mcg/kg/day doses of odevixibat demonstrated superiority to the placebo arm (Table 4). The results for the alternative endpoint considered by FDA (see Primary Efficacy Endpoints section and Table 4) were consistent with the primary efficacy analysis that treatment with odevixibat is more effective than placebo (i.e., the FDA alternative endpoint definition resulted in a one-sided unadjusted p-value of 0.0069 for 40 mcg/kg/day and 0.0390 for 120 mcg/kg/day).

Table 4: *Efficacy Results Over 24-Week Treatment Period in Trial A4250-005.**

Results	Placebo n=20	Odevixibat 40 mcg/kg/day n=23	Odevixibat 120 mcg/kg/day n=19
Prespecified primary endpoint definition: Mean percentage of assessments that are ≤1 or at least a 1-point drop from baseline			
LS mean (SE)	30.1 (9.1)	58.3 (8.6)	51.8 (9.5)
95% CI for LS mean difference		(9.8, 46.6)	(1.9, 41.5)
One-sided unadjusted p-value		0.0016	0.0163
FDA alternative endpoint definition: Mean percentage of assessments that are ≤1			
LS mean (SE)	13.2 (8.7)	35.4 (8.1)	30.1 (9.0)
95% CI for LS mean difference		(4.7, 39.6)	(-2.0, 35.7)
One-sided unadjusted p-value		0.0069	0.0390

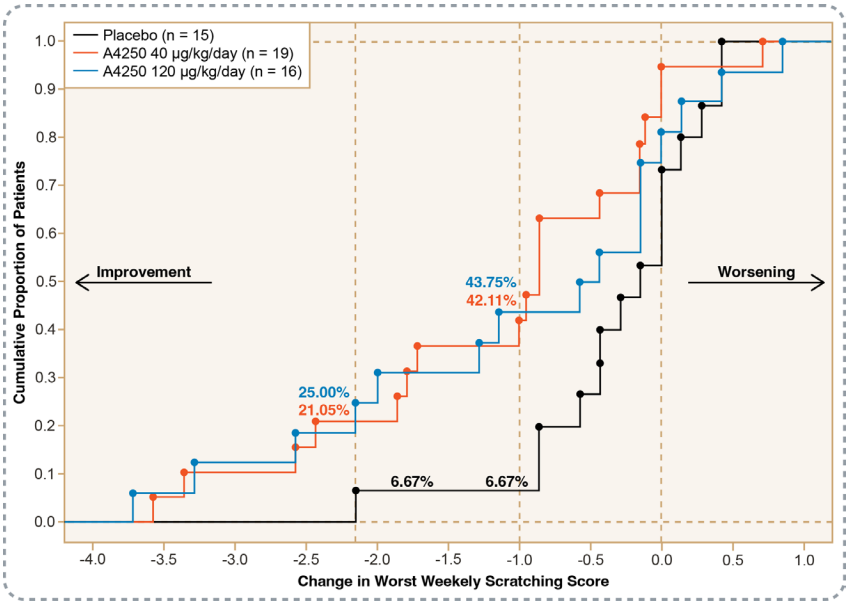
** Results presented for the randomized set as intent-to-treat (ITT) population.*

2. **Clinically meaningful within-participant change:** Additional evidence of treatment benefit was provided by evaluating the Worst Weekly Scratching Score. Both odevixibat doses yielded meaningful within-participant improvement in scratching severity relative to placebo.
3. **Consistent benefit across centers:** Each of the 33 centers contributed an average of one to two participants and the efficacy results were not driven by one center or one region.

Interpretation of Efficacy Results

- Clear separation between the two odevixibat treatment arms and the placebo arm showing decreases (improvement) in Worst Weekly Scratching Score of 0 or more, with clear and notable separation within the range of thresholds for meaningful improvement of (-2.14, -1) (Figure 4).
- Notable overlap between the low and high doses of odevixibat, especially among participants who experienced a decrease (improvement) in Worst Weekly Scratching Score of 1 point or more (Figure 4).

Figure 4: *eCDF plot of Change in Worst Weekly Scratching Score from Baseline (Study Days [-28, -1]) to Weeks 21-24 (Study Days [141, 168]) by study arm among participants with complete Worst Weekly Scratching Score data at both Baseline and Weeks 21-24 (n=50, Trial A4250-005 FAS. Figure 4 was generated using information provided on page 233 of the Integrated Review (Figure 39) for odevixibat (Bylvay), NDA 215498.*



Substantial Evidence of Effectiveness: Confirmatory Evidence

The confirmatory evidence for odevixibat for the treatment of pruritus included evidence of reduction of serum bile acids (sBA) in a phase 2 trial, and nonclinical proof-of-concept evidence.

For more information about the confirmatory evidence, please refer to the Integrated Review.

Key Takeaways:

The Development and Use of COAs

The main source of evidence to demonstrate substantial evidence of effectiveness of odevixibat for the treatment of pruritus in PFIC came from one randomized, double-blind, placebo-controlled, adequate and well-controlled investigation plus confirmatory evidence.

Essentially:

a. The overall findings were statistically persuasive.
b. Consistent benefit across clinical study centers was observed.
c. Clinically meaningful within-participant changes were observed.

Specifically:

- Primary efficacy endpoints were based on novel ObsRO measures of pruritus.
- To support the validity of the COAs the Applicant conducted a targeted literature review, collected input from clinicians with PFIC expertise, conducted patient and caregiver interviews, and conducted quantitative analyses.
- Additionally, in patient listening sessions organized by the FDA, families and caregivers of patients with PFIC confirmed that pruritus is a disabling symptom and can be severe and unrelenting, adversely affecting the quality of life of both children with PFIC and their caregivers.
- The outcome of these activities confirmed that pruritus was the most common and relevant symptom in patients with PFIC.
- General alignment was noted between patient-reported itching severity and caregiver-reported scratching severity among the nine participants (aged 8 to 18 years) with both PRO and ObsRO score data available at Baseline. Although some uncertainty surrounds these findings due to the very small sample size available (n=9), these results supported the use of caregiver-reported scratching severity to evaluate treatment effects.

Conclusion

For this trial, the Applicant developed two novel COAs – an ObsRO and a PRO – using input from the patient community. Treatment with odevixibat demonstrated statistically persuasive and clinically meaningful results in improvement of pruritus.

Critical Thinking Questions for a Rare Disease Drug Development Program

When planning for and designing a clinical investigation(s) for a rare disease medical product, we encourage the use of this case study as a resource to inform questions and engagement with the FDA. When it is determined that the clinical trial will require developing a novel COA, consider the following:

1. How does the plan ensure the concept(s) of interest of a COA(s) is/are relevant to the patients with the rare disease, caregivers, and clinical experts?
2. How would the plan integrate patient perspectives into the development and selection of COA(s)?
3. How will the development plan generate evidence supporting the validity of the COA(s)?
4. How does the development plan to compute primary efficacy endpoints based on the data collected using the COA(s)?

We recommend meeting with the Agency early in development to reach alignment regarding the design of the COA and primary efficacy endpoints.

Additional Resources

1. Guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Collecting Comprehensive and Representative Input* (June 2020). https://www.fda.gov/media/139088/download
2. Guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Methods to Identify What Is Important to Patients* (February 2022). https://www.fda.gov/media/131230/download
3. Draft guidance for industry, Food and Drug Administration staff, and other stakeholders *Patient-Focused Drug Development: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision Making* (April 2023). https://www.fda.gov/media/166830/download. When final, this guidance will represent the Agency's current thinking on this topic.
4. Rare Disease Clinical Outcome Assessment Consortium. https://c-path.org/program/rare-disease-clinical-outcome-assessment-consortium/

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 FDA Integrated Review document for odevixibat (Bylvay) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215498Orig1s000IntegratedR.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* (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.

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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 the FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource available at https://www.ncbi.nlm.nih.gov/books/NBK326791/.

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- See draft guidance for industry *Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessment* (June 2022) available at https://www.fda.gov/media/159500/download. When final, this guidance will represent the Agency's current thinking on this topic.
- See FDA's Patient-Focused Drug Development Glossary available at https://www.fda.gov/drugs/development-approval-process-drugs/patient-focused-drug-development-glossary.
- See the FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource available at https://www.ncbi.nlm.nih.gov/books/NBK326791/.

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- See page 31 of the FDA Integrated Review document for odevixibat (Bylvay) for more information on trial design available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215498Orig1s000IntegratedR.pdf.

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- See the FDA Integrated Review document for odevixibat (Bylvay) for more information about the confirmatory evidence available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215498Orig1s000IntegratedR.pdf.