CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215498Orig1s000

OTHER REVIEW(S)

COA Tracking ID:
IND Number:

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2020518
NDA#:	130591
Sponsor:	Albireo AB
Established Name/Trade Name:	Odevixibat
Indication:	Progressive Familial Intrahepatic Cholestasis (PFIC) (b) (4) ☒Rare Disease/Orphan Designation ☒Pediatrics
Meeting Type:	N/A
Review Division:	Division of Hepatology and Nutrition
Clinical Reviewer	Ruby Mehta
Clinical Team Leader (TL)	Yao-Yao Zhu
Regulatory Project Manager:	Ayanna Augustus
COA Reviewer:	Yujin Chung
COA TL:	David Reasner
COA Deputy Director (Acting):	Elektra Papadopoulos, MD, MPH
COA Director:	David Reasner, PhD
Date Consult Request Received:	12/2/2020
Date COA Briefing Package/Submission Received:	11/20/2020
Instruments reviewed:	Pruritus measure item ☒ Observer-reported outcome (ObsRO)
	Pruritus measure item ☒ Patient-reported outcome (PRO)

1. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to NDA 130591 for odevixibat. The proposed indication is Progressive Familial Intrahepatic Cholestasis (PFIC) (b) (4)

Study A4250-005 (PEDFIC 1) was a double-blind, randomized, placebo-controlled, phase 3 study to assess the efficacy and safety of odevixibat compared to placebo in children with PFIC. Pediatric patients between the ages of 6 months to 18 years with PFIC 1 or PFIC 2 were included. The study consisted of a 24-week treatment period with a 4-week follow-up period.

The primary efficacy endpoint in study A4250-005 was:

- The proportion of positive pruritus assessments at the patient level over the 24- week treatment period. A positive pruritus assessment is defined as a scratching score of ≤1 or at least a 1-point drop from baseline on the Albireo ObsRO instrument

The review concludes the following:

- The evidence submitted by the applicant is sufficient to demonstrate that the Pruritus Measure Item is fit-for-purpose[1] to measure itching and scratching for the context of use of this drug development program.

2. Clinical Outcome Assessment Review

This review focuses on the applicant's Patient Reported Outcome (PRO) and Observer Reported Outcome (ObsRO) measures of pruritus.

Proposed COAs Included in Study

COA Name (COA Type)	Concept(s)	Endpoint Position	Assessment Frequency
Pruritus Measure Item (ObsRO)	Scratch	Primary	Twice daily
Pruritus Measure Item (PRO)	Itch	Secondary	Twice daily

ObsRO= Observer-reported outcome; **PRO=** Patient-reported outcome

Clinical Outcome Assessment Instruments

[1] Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; https://www ncbi.nlm nih.gov/books/NBK338448/)

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Clinical Outcome Assessment Description

The ObsRO measure of scratching severity

- The ObsRO item 1 is designed to assess scratching severity on a 5-point numeric rating scale that includes correlating facial expressions ranging from 0 ("no scratching") to 4 ("the worst possible scratching"). The recall period is over the previous half day (e.g., since he/she went to bed last night, since he/she woke up this morning).

The PRO measure of itching severity

- The PRO item 1 is designed to assess itch intensity on a 5-point numeric rating scale that includes correlating facial expressions ranging from 0 ("no itching") to 4 ("the worst itching"). The recall period is over the previous half day (e.g., since you went to bed last night, since you woke up this morning).

Conceptual Framework

Conceptual Framework of ObsRO Pruritus Item

Item	Domain	General Concept
How bad was your child's worst scratching since he/she went to bed last night?	Nighttime Scratching	Daily Scratching
How bad was your child's worst scratching since he/she woke up this morning?	Daytime Scratching	

Conceptual Framework of PRO Pruritus Item

Item	Domain	General Concept
How bad was your worst itching since you went to bed last night?	Nighttime Itching	Daily Itching
How bad was your worst itching since you woke up this morning?	Daytime Itching	

Content Validity

Pruritus Measure Items (ObsRO and PRO)

- **Literature review:** The applicant completed a targeted literature search using public databases to identify the signs, symptoms and impacts of PFIC with a focus on cholestatic pruritus. Pruritus was the most common symptom identified in the literature (*Bergasa N, Mehlman J & Jones E. "Pruritus and fatigue in primary biliary cirrhosis." In Bailliere's Best Practice & Research: Clinical Gastroenterology, 2000, 643-655*). We agree that pruritus is an important and relevant concept in cholestatic pruritus diseases. This conclusion is also supported by patient interview data, and pruritus is a debilitating symptom brought up in past public patient focused drug development meetings.

- **Documentation of expert input**: Expert input was gathered from five clinicians with PFIC expertise. Three clinicians' interviews focused on PFIC symptoms, and the other two interviews focused on sleep disturbance. Clinicians confirmed the literature review findings and the importance of pruritis in PFIC patients. They also emphasized that pruritus is most troublesome when a child goes to bed.
- **Patient and caregiver interviews:** The applicant conducted two sets of interviews (stage I and stage II) with a total number of 36 interviews with 28 patients and caregivers across the stages, and 8 patients and caregivers interviewed in both stages I and II. Each Stage I interview comprised of a concept elicitation and a cognitive debriefing segment.

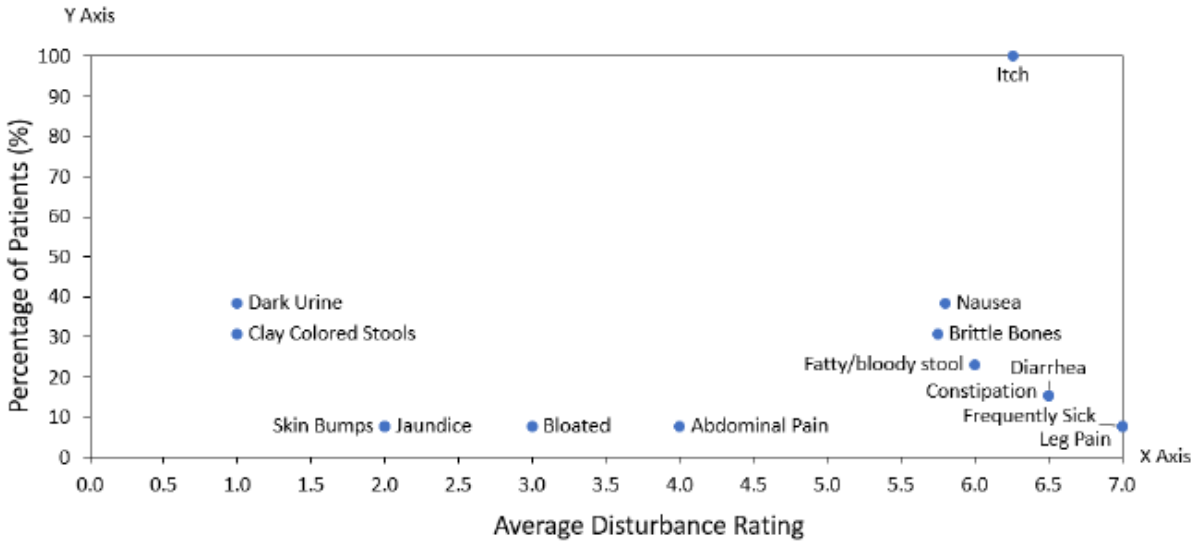
  The objectives of stage I and II interviews were:
  1) To identify the most relevant pediatric PFIC and cholestatic liver disease signs, symptoms and impacts for patients
  2) To evaluate patient/caregiver understanding of the draft instrument instructions, items, and response scales and to refine the draft PRO and ObsRO measures
  3) To determine the appropriate age at which pediatric patients with PFIC and other cholestatic liver diseases can begin to self-report

  Patient selection inclusion and exclusion criteria for interviews:

  - Inclusion Criteria
    - Diagnosis of PFIC, Alagille Syndrome, Biliary Astresia or Primary Sclerosing Cholangitis
    - Diagnosis of cholestatic pruritus
    - Patient or caregiver report of pruritus "Sometimes", "Most of the time" or "All of the time"
    - Age $\leq$ 18 years
    - Resides in the United States, Canada, United Kingdom, or Australia
    - Any education level
  - Exclusion Criteria
    - Previous liver transplantation
    - Has a family member currently affiliated with the FDA or a government agency that approves medications, advertising agency, marketing research company, or pharmaceutical or biotechnology company

  The frequency and average disturbance of each symptom reported from the patient/caregiver interviews are displayed below

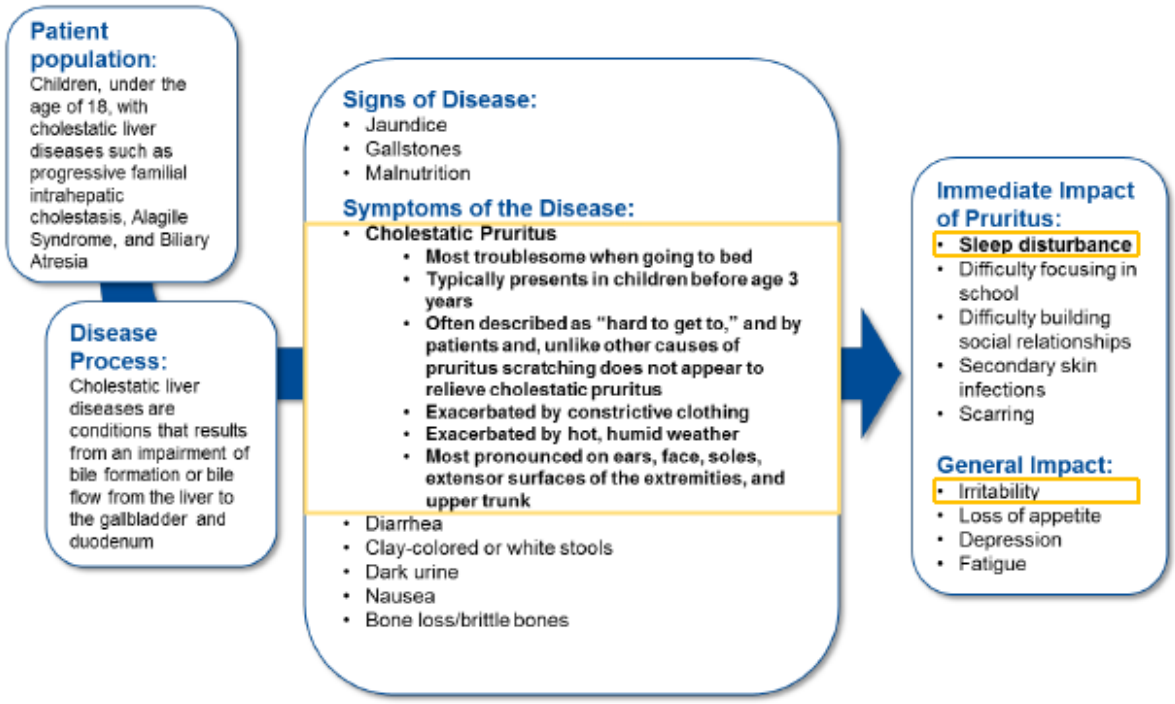
Figure 2: Sign and Symptom Frequency vs. Average Disturbance (Study A4250-005)



Note: Based on sample of n = 13 (disturbance ratings not obtained during 2 patient interviews).

The applicant updated their conceptual model after the concept elicitation interview findings. The impact that pruritus had on sleep was also considered to be highly disruptive because it often interfered with both the sleep of the child and of the family. Subsequently, many caregivers reported that their children were highly irritable as a result of fatigue and constant pruritus. This irritability was therefore added to the conceptual model as a general impact.

Figure 4: Conceptual Model Following Stage I Interviews (Study A4250-005)



A summary of the results is described below:

- The stage I concept elicitation interview results confirmed that pruritus is the most frequent symptom that is experienced by patients with PFIC and other cholestatic liver diseases. Itch was reported in 100% of patients.
- Itch was the only symptom to be reported by more than 50% of respondents and it received an average disturbance rating of 7.3. The other most frequently reported signs and symptoms were dark urine (38%), nausea (38%), clay colored stools (30%), and bone loss/brittle bones (30%).
- Itch most frequently occurred at night. Parents also reported that their children verbally tell them they are itchy or ask to be scratched and that they observe visible signs of scratching such as marks on the child's skin or blood on their bedsheets. Clinical also agreed that itch fluctuations can be worse at nighttime.
- Stage I and II cognitive interviews resulted in retaining faces in the pictorial scale, and card sorting exercises were done by pediatric patients ($\geq$ 6 years of age) who were able to correctly sort the severity of the response options in order from "feeling ok" to "feeling the worst". The applicant demonstrated that children 6 years and older may have the ability to reliably differentiate the scratching severity according to the pictorial scale. However, the administration of the PRO measure was decided to be administered in patients 8 years of age and older due to some of the 7 and 6-year-old patients having difficulty responding to the PRO measure. We agree with the PRO age of administration due to other pediatric data in drug development programs and recommendations from literature guidelines.
- We acknowledge and agree that itch is the most frequent and important symptom to assess for improvement in patients with cholestatic liver diseases and item 1 of

the itch instruments (PRO and ObsRO) are reasonable tools to assess the severity of pruritis in these patients.

Anchor Scales (Single-item Global Measures)

Symptom Severity

- Patient Global Impression of Symptoms (PGIS)
- Caregiver Global Impression of Symptoms (CaGIS)
- Clinician Global Impression of Symptoms (CGIS)

The symptom severity global measures are a single item instrument that assesses the overall symptom severity in the patient's itching or scratching at the time of assessment and with reference to the recall period. Note that the recall period is "over the past week". There are 5 response options for the verbal rating scale (none, mild, moderate, severe, very severe). Screenshots of the global measures are available in COA Appendix 6.

Symptom Change

- Patient Global Impression of Change (PGIC)
- Caregiver Global Impression of Change (CaGIC)
- Clinician Global Impression of Change (CGIC)

The symptom change global measures are a single item instrument that assesses the overall change in the patient's itching or scratching at the time of assessment compared to since starting the study. There are 7 response options for the verbal rating scale (very much better, much better, a little better, no change, a little worse, much worse, very much worse). Screenshots of the global measures are available in COA Appendix 6.

Reviewer's notes: As a joint collaborative effort with multiple disciplines including PFSST and Biostatistics, the review team has suggested the exploratory efficacy endpoint of "change in worst weekly scratching score from baseline to weeks 21–24" to facilitate in assessing clinically meaningful within-patient change aligned with the recall period of 1 week on the anchor scale, CaGIS.

Exit Survey

The applicant conducted exit surveys in an attempt to provide supportive data on assessing meaningful change in patients, and to provide supportive evidence in addition to the anchor-based methods discussed. The survey included 7 patients $\geq$ 8 years old, and 42 caregivers (30 on treatment and 12 placebo).

Survey Questions:

1. Have you or your child experienced change from the study drug at the end of the study? Yes/No

2. Was the change meaningful? Yes/No
3. In what way was the change meaningful?

Summary of Exit Survey as Reported by Caregivers (Full Analysis Set)

PARAMETER	PLACEBO N=20 n (%)	ODEVIXIBAT, ONCE DAILY DOSING		
		40 µg/kg N=23 n (%)	120 µg/kg N=19 n (%)	ALL DOSES N=42 n (%)
Number of Caregivers answering Exit Survey[a]	12	16	14	30
Q1 and Q2 = Yes: Change experienced and considered meaningful	4 (33.3)	13 (81.3)	8 (57.1)	21 (70.0)
Q1 = Yes and Q2 = No: Change experienced and not considered meaningful	1 (8.3)	0	0	0
Q1 = No: No change experienced	7 (58.3)	3 (18.8)	6 (42.9)	9 (30.0)

[a] The percentage is calculated based on the number of caregivers/patients with the exit survey answered.

Q1: Have you or your child experienced change from the study drug at the end of the study?

Q2: Was the change meaningful?

Reviewer's notes: Meaningful change was reported in 70.0% of patients, (including 81.3% and 57.1% of patients in the 40 and 120 µg/kg/day groups, respectively, compared with 33.3% of patients who received placebo)
The data suggest that there were more patients that experience meaningful change in the treatment arm and less for those in the placebo arm

Summary of Change from Baseline in Pruritus Score in the last 2 Weeks for Patients having an Answer "YES" for Exit Survey Questions 1 and 2

Visit Statistics	Albireo ObsRO Instrument		
	AM and PM Score	AM Score Only	PM Score Only
Baseline			
n	25	25	25
Mean (SE)	2.98 (0.107)	3.02 (0.089)	2.94 (0.127)
Median	3.00	3.00	3.00
Min, Max	1.9, 3.9	2, 3.9	1.6, 4
Last 2 Weeks			
n	25	24	25
Mean (SE)	1.58 (0.198)	1.69 (0.209)	1.54 (0.190)
Median	1.81	1.85	1.71
Min, Max	0, 4	0, 4	0, 4
Change from Baseline			
n	25	24	25
Mean (SE)	-1.40 (0.223)	-1.33 (0.235)	-1.40 (0.219)
Median	-1.22	-1.29	-1.31
Min, Max	-3.8, 0.9	-3.6, 0.9	-4, 0.9

<u>Reviewer's notes</u>: For those patients reported to have a meaningful change, mean changes from baseline to the last 2 weeks of treatment were -1.40 for AM and PM pruritus scores combined, -1.33 for AM scores, and -1.40 for PM scores.

Visit Statistics	Albireo ObsRO Instrument		
	AM and PM Score	AM Score Only	PM Score Only
Baseline			
n	17	17	17
Mean (SE)	2.96 (0.139)	3.05 (0.145)	2.87 (0.147)
Median	2.89	2.93	2.93
Min, Max	2, 4	2, 4	1.9, 4
Last 2 Weeks			
n	17	17	17
Mean (SE)	2.99 (0.244)	3.08 (0.244)	2.90 (0.255)
Median	3.00	3.36	3.00
Min, Max	0.4, 4	0.3, 4	0.5, 4
Change from Baseline			
n	17	17	17
Mean (SE)	0.02 (0.194)	0.03 (0.203)	0.03 (0.201)
Median	0.10	0.14	0.00
Min, Max	-1.8, 1.1	-2, 1.4	-1.5, 1.7

<u>Reviewer's notes</u>: For patients without a meaningful change noted, mean changes from baseline to the last 2 weeks of treatment were 0.02 for AM and PM pruritus scores combined, 0.03 for AM scores, and 0.03 for PM scores. This difference appears smaller compared to the change from baseline from the patients who reported meaningful change.

In both the ObsRO and PRO versions of the instrument, patients who answered "yes" to the exit survey questions 1 and 2, reported lower pruritus scores (lower score indicating less pruritus severity) compared to patients who answered "no" who reported overall higher pruritus scores. The exit survey data look reasonable from a qualitative standpoint, but a definitive conclusion is also necessarily based on quantitative interpretation.

Reviewer's notes: PFSST has informed DCOA on their perspective on the limitations of the exit surveys. The question on experiencing "change" may be either improvement or worsening, and it is unclear who is providing the responses to question #3 (many responses appear to be provided by a clinician rather than the patient or a caregiver).

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Templates
Version: 2018-01-24

Date:	July 12, 2021
Reviewer:	Joel L. Wessfeld, MD MPH Division of Epidemiology I
Acting Team Leader:	Catherine Lerro, PhD MPH Division of Epidemiology I
Deputy Director:	CAPT. Sukhminder K. Sandhu, PhD MPH MS Division of Epidemiology I
Subject:	Maternal and fetal outcomes
Drug Name:	odevixibat (Bylvay)
Application Type/Number:	NDA 215498
Submission Number:	eCTD 0001
Applicant/sponsor:	Albireo AB
OSE RCM #:	2021-399

U.S. FOOD & DRUG ADMINISTRATION

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

NDA 215498 seeks approval for odevixibat as a treatment for pruritus in patients with Progressive Familial Intrahepatic Cholestasis (PFIC) (b) (4). PFIC 1 and 2 are rare (one in 50,000 to 100,000 births) autosomal recessive disorders of ATP8B1 (phospholipid-transporting ATPase IC, ATP8B1) and ABCB11 (bile salt export pump, BSEP), respectively. ATP8B1 and BSEP are two proteins used by liver cells to secrete bile acids. Persons with severe ATP8B1 (PFIC1) or BSEP (PFIC2) deficiency develop jaundice and pruritus with onset during the first year of life and variable progression to liver failure.

Odevixibat is a reversible inhibitor of the ileal bile acid transporter (IBAT). Odevixibat reduces serum bile acids and improves pruritis by interrupting enterohepatic bile acid circulation. Odevixibat is a poorly absorbed orally administered drug with 2.4-hour mean elimination half-live in healthy adults. Pharmacologic assessments in healthy adults indicate that measurable systemic drug concentrations might occur at exposures toward the upper end of the recommended dose range.[a]

1.2. Describe the Safety Concern

NDA 215498 presents results from (1) studies of oral odevixibat on embryo-fetal development in rabbits and rats and (2) a study of postnatal development in rats born to mothers orally dosed with odevixibat during organogenesis through lactation.[b] As summarized in the approved label for odevixibat, the embryo-fetal development study in rabbits showed increased incidence of fetal cardiovascular malformation at low maternal systemic exposure.

The Division of Pediatric and Maternal Health (DPMH) reviewed the medical literature to document six instances of pregnancy in women with PFIC .[c] DPMH's review of NDA 215498 and medical literature identified no instances of human exposure to odevixibat during pregnancy. Therefore, the Pregnancy Risk Summary for the approved odevixibat label indicates that "[t]here are no human data on BYLVAY use in pregnant persons to establish a drug-associated risk of major birth defects, miscarriage, or adverse (b) (4) outcomes." Background risk of major birth defects and miscarriage for PFIC also has not been-characterized, though elevated maternal serum bile acids are associated with adverse fetal outcomes including intrauterine demise, meconium amniotic fluid, preterm delivery, and neonatal respiratory distress syndrome.[d]

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[a] Integrated Review for BYLVAY (odevixibat) NDA 215498, Section 5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology.

[b] Limpert J, M Dinatale, and LP Yao, Division of Pediatric and Maternal Health Review, filed under NDA 215498 on April 14, 2021 (DARRTS Reference ID: 4778551).

[c] Ibid., pp 3-4.

[d] Ibid, p 4.

Responding to concern in the Division of Hepatology and Nutrition (DHN) about the finding of cardiovascular malformation in fetal rabbits (described above), DPMH agreed to a post-market requirement (PMR) for a descriptive study of odevixibat safety in pregnancy.[e] As noted above, supportive rationale for this PMR study derives from (1) a non-clinical study showing teratogenicity at low maternal systemic exposures to odevixibat, (2) clinical pharmacology evidence for measurable systemic drug concentrations at drug exposures toward the upper end of the recommended dose range, and (3) case reports demonstrating that women with PFIC can become pregnant. DPMH assessed the PMR request from DHN as "reasonable because there are currently no available human data to inform the safety of odevixibat during pregnancy."[f]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☒ No approved indication, but practitioners may use product off-label in pregnant women (e.g., pregnant women with PFIC 3 or intrahepatic cholestasis of pregnancy)

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized in women with PFIC or intrahepatic cholestasis of pregnancy

☒ No approved indication, but use in women of childbearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

☐ Pregnancy registry with internal comparison group

☐ Pregnancy registry with external comparison group

[e] Limpert J, M Dinatale, and LP Yao, Memorandum to File, filed under NDA 215498 on July 1, 2021 (DARRTS Reference ID: 4819024.

[f] Ibid., p 2.

☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☐ Electronic database study without chart review (*e.g.*, retrospective cohort study using claims or electronic medical record data or a case-control study nested in a pre-existing pregnancy or birth defect registry)
☒ Other, please specify: A descriptive pregnancy safety study, defined as a protocol-driven uncontrolled (single-arm) observational cohort study that collects detailed data for descriptive analysis. FDA might require a descriptive pregnancy safety study (known in draft FDA Guidance as a pregnancy surveillance program) "when the likelihood of exposure in pregnancy is low."[g] Most PFIC patients develop end-stage liver disease and undergo liver transplantation before reaching sexual maturity. Consequently, the PFIC treatment setting (infrequent drug exposure expected in pregnant women) precludes meaningfully powered comparative analysis and negates any requirement for a preset sample size.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☒ Study Population
☒ Exposures
☒ Outcomes
☒ Covariates
☐ Analytical Tools

For any checked boxes above, please describe briefly:

Study Population:

- DHN requests a study population defined as females of child-bearing age exposed to odevixibat during pregnancy and/or lactation. The Sentinel Distributed Database (SDD) does not permit accurate identification of lactating women.
- PFIC 1 and 2 are uncommon genetic conditions. Therefore, DHN requests a worldwide study to provide an adequate number of exposed patients for meaningful risk assessment. The SDD covers a portion of the U.S. population.

Exposures/Outcomes/Covariates: A descriptive pregnancy safety study requires targeted questionnaires for collection of detailed and specific information about important confounders (e.g., body mass index and illicit drug use) and the timing of drug exposures in relation to well-defined pregnancy outcomes. Data elements considered appropriate for collection by targeted questionnaire (per FDA guidance) include drug or biological product exposures and results from neonatal physical examinations. Data collection should occur at pre-determined intervals (e.g., at study enrollment, mid-point of pregnancy, estimated delivery date, 3-6 months postpartum, and 12 months postpartum). A series of well-documented case narratives that present detailed clinical information acquired directly from primary sources (*e.g.*, medical records and providers) might permit credible assessment of the causal significance of an adverse event associated with odevixibat exposure during pregnancy. The requirement for targeted questionnaires necessitates data collection not possible in SDD.

[g] FDA Draft Guidance, *op. cit.*

2.5. Please include the proposed PMR language in the approval letter.

Conduct a worldwide descriptive study that collects prospective and retrospective data in females of child-bearing potential who are prescribed BYLVAY (odevixibat) during pregnancy and/or lactation to assess risk of maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The study will collect information for a minimum of 10 years.

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
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Memorandum to File - Addendum to the April 8, 2021 DPMH Review

Date: June 25, 2021 **Date consulted:** December 2, 2020

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Hepatology and Nutrition (DHN)

Drug: Bylvay (odevixibat)

NDA: 215498

Applicant: Albireo AB/Albireo Pharma, Inc.

Subject: Input for Postmarketing Requirements (PMRs)

Proposed Indication: Treatment of pruritis in pediatric patients (age (b)(4) 3 months to 17 years) with progressive familial intrahepatic cholestasis (PFIC)

BACKGROUND

On November 20, 2020, Albireo AB submitted a 505(b)(1) New Drug Application (NDA) for Bylvay (odevixibat), a new molecular entity. The proposed indication is for

the treatment of pruritis in pediatric patients with PFIC. On December 2, 2020, DHN consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

Pregnancy in patients with PFIC is rare; the published literature reports only six cases of pregnancy in patients with PFIC. There are no available data on odevixibat use in pregnant persons. In embryofetal studies, pregnant rabbits exposed to oral odevixibat during organogenesis had a corresponding increase in fetal cardiac malformations at low maternal systemic exposures and a no adverse event level (NOAEL) could not be established. The team agreed to add language in Subsection 8.1 that based on animal studies, odevixibat may lead to cardiac malformations. DPMH did not recommend PMRs for pregnancy and lactation due to the rarity of this disease and because patients are typically treated with odevixibat in childhood prior to surgical intervention and/or liver transplantation. The reader is referred to the April 2021 DPMH Bylvay consult for additional details.

On June 23, 2021, DHN reached out to DPMH regarding a PMR for a descriptive pregnancy safety study (DPSS) based on the adverse findings of cardiac malformations in the rabbit embryofetal studies.

DISCUSSION

While pregnancy in PFIC is rare, it is possible for patients with PFIC to become pregnant. Based on the fetal cardiac malformations observed in animal reproduction studies, there may be risks to the fetus from exposure to odevixibat during pregnancy. DPMH agrees that collecting postmarketing information to assess maternal and fetal outcomes in patients with PFIC who become pregnant while undergoing treatment with odevixibat is reasonable because there are currently no available human data to inform the safety of odevixibat during pregnancy.

CONCLUSIONS

DPMH agrees with DHN’s plan to issue a PMR for a DPSS.

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/s/

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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 22, 2021
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 215498
Product Name and Strength:	Bylvay (odevixibat) (b) (4), 400 mcg and 1200 mcg Bylvay (odevixibat) oral pellets, 200 mcg and 600 mcg
Applicant/Sponsor Name:	Albireo
OSE RCM #:	2020-2448-2
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 21, 2021 for Bylvay. Division of Hepatology and Nutrition (DHN) requested that we review the revised container labels and carton labeling for Bylvay (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are acceptable from a medication error perspective and we have no additional comments at this time.

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[a] Abraham, S. Label and Labeling Review for Bylvay (NDA 215498). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 15. RCM No.:2020-2448-1

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SHERLY ABRAHAM
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IDALIA E RYCHLIK
06/22/2021 03:58:10 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	June 15, 2021
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 215498
Product Name and Strength:	Bylvay (odevixibat) (b) (4), 400 mcg and 1200 mcg Bylvay (odevixibat) oral pellets, 200 mcg and 600 mcg
Applicant/Sponsor Name:	Albireo
OSE RCM #:	2020-2448-1
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on June 10, 2021 for Bylvay. Division of Hepatology and Nutrition (DHN) requested that we review the revised container labels and carton labeling for Bylvay (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. We have provided recommendations in Section 3 for the for the for the Applicant. We ask that the Division convey Section 3 in its entirety to Albireo so that recommendations are implemented prior to approval of this NDA.

3 RECOMMENDATIONS FOR ALBIREO

We recommend the following be implemented prior to approval of this NDA:

[a] Abraham, S. Label and Labeling Review for Bylvay (NDA 215498). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 JUN 4. RCM No.:2020-2448

Identified Issues and Recommendations for Albireo (entire table to be conveyed to Applicant			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As currently presented, the strength statements across all product strengths utilize the same color scheme.	We note that in your June 10, 2021, response document, container labels, and carton labeling, you revised the strength statements to be in (b) (4) We recommend the proprietary name and strength statements to appear in its own unique color and the color does not overlap with other colors utilized in highlighting other product strengths. We recommend this to differentiate between the strengths and to prevent wrong strength selection errors.	Differentiate the strength presentation across the product line. Consider revising the strength statements to align with the color schematic of the label and labeling. For example, use (b) (4) for the 200 mcg statement, use (b) (4) for the 400 mcg statement, use (b) (4) for the 600 mcg statement, and use (b) (4) for the 1,200 mcg statement. We refer to our previous label and labeling recommendations communicated on June 8, 2021 regarding the font color of the proprietary name (b) (4) and established name (b) (4) . Ensure these colors do not overlap with any of the strength font color presentations. Consider revising the proprietary name and established name font to black .
Container Labels			
2.	The "Rx only statement" is overly prominent.	The increased prominence of the "Rx only statement" takes the reader's attention away from other important information on the PDP such as proprietary and established name, dosage form, and strength statements.	Decrease the prominence of the "Rx only statement" by decreasing the font size similar to the NDC number and relocate the statement to a bottom right corner of the principal display panel (PDP).

Identified Issues and Recommendations for Albireo (entire table to be conveyed to Applicant			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
3.	The 'Rx only' statement is in close proximity to the strength statement.	The close proximity of the "Rx only statement" to strength statement takes the reader's attention away from other important information on the PDP such as strength statement, proprietary name, established name, and dosage form statement.	Relocate the 'Rx only' statement to the top left corner of the PDP.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	June 4, 2021
Requesting Office or Division:	Division of Hepatology and Nutrition (DHN)
Application Type and Number:	NDA 215498
Product Name and Strength:	Bylvay (odevixibat) (b) (4), 400 mcg and 1200 mcg Bylvay (odevixibat) oral pellets, 200 mcg and 600 mcg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Albireo
FDA Received Date:	December 22, 2021, May 3, 2021
OSE RCM #:	2020-2448
DMEPA Safety Evaluator:	Sherly Abraham, R.Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

As part of the approval process for Bylvay (odevixibat) oral pellets and capsules, the Division of Hepatology and Nutrition (DHN) requested that we review the proposed Bylvay Prescribing Information (PI), Instructions for Use (IFU), carton labeling, and container labels for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
ISMP Newsletters	C-N/A
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Information Request	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

The proposed PI, IFU, container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide specific recommendations, our rationale for concern, and the proposed recommendation to minimize the risk for medication error in Section 4.1 for the Division and in Section 4.2 for Albireo.

As proposed, the PI utilizes overly complex dosage-form-dependent, weight-based dosing instructions. The Sponsor initially proposed that for patients weighing less than 19.5 kilograms only the oral pellet dosage form was indicated for use verses for patients weighing 19.5 kilogram or more only the capsule dosage form should be utilized. Hence, throughout the review process, we engaged in multiple information requests (IR) with the Sponsor to assess the necessity of dosage-form-dependent prescribing restrictions (see Appendix E). We requested additional information from the Sponsor regarding the following:

1. What the clinical implications outcomes are if wrong dosage form error and/or wrong strength errors occur?
2. What the safety outcomes are if wrong dosage form error and/or wrong strength errors occur?

3. The need for the Sponsor to develop an IFU to communicate important preparation and administration information to patients and caregivers.

In their responses to our IRs, the Sponsor confirmed no negative outcomes, in terms of clinical response or effectiveness, in the event that wrong technique in dose preparation and/or wrong dosage form errors were to occur (i.e. the oral pellet were to be swallowed whole or the capsule were to be opened and mixed with food for administration). Additionally, the Sponsor confirmed that both dosage forms (capsules and oral pellets) are substitutable for each other and product strengths (200 mcg, 400 mcg, 600 mcg, and 1200 mcg) (b) (4)

We note that the although the Sponsor confirmed that there are no clinical, safety or efficacy concerns associated with errors pertaining to the prescribing of the wrong dosage form and/or dose preparation and administration errors, the oral pellets, due to the large capsule size, are not intended to be swallowed whole. The capsule size utilized for the oral pellet may present swallowability and choking concerns for infants and pediatric patients. We defer to the clinical team and the Division of Pediatric and Maternal Health (DPMH) for the appropriateness of the proposed oral pellet capsule size.

4 CONCLUSION

Our evaluation of the proposed prescribing information (PI), Instructions for Use (IFU), carton labeling, and container labels identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Section 4.1 for the for the Division and Section 4.2 for the Applicant. We ask that the Division convey Error! Reference source not found. 4.2 in its entirety to Albireo so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF HEPATOLOGY AND NUTRITION (DHN)

A. Prescribing Information

1. Highlights of Prescribing Information: Section 2 Dosage and Administration

   Recommendations are noted in tracked changes below to improve readability and clarity of statements:

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage is 40 mcg/kg once daily.
- If there is no improvement observed in pruritus after 3 months, the dosage may be increased in 40 mcg/kg increments up to a maximum dose of 120 mcg/kg once daily.

Administration:

- Administer BYLVAY in the morning with (b) (4)
- Do not crush or chew capsules.
- See prescribing information for administration instructions. (2.2)

2. Full Prescribing Information: Section 2.1 Recommended Dosage
    a. The recommended dosage statement, "The recommended dosage of BYLVAY is 40 mcg/kg once daily" is missing critical information such as the time of day when the dose should be administered and correct administration instruction. We recommend adding to the dosage statement, "in the morning with meals".
    b. The second bullet referring to the dose increase after 3 months (b) (4) discussed by the DHN during previous labeling meetings. If this intermediate dose is to be approved, we recommend the following revision to the dosage statement : "If (b) (4) after 3 months, the dosage may be increased in increments of 40 mcg/kg up to (b) (4) of 120 mcg/kg once daily."
    c. Important dosing parameters (i.e. weight range and indicated dosage forms) are presented within the heading of Administration Instructions. We recommend adding this important information as separate bullets for improved readability and avoid overlooking this important dosage information.
    d. The applicant has confirmed that both dosage forms (capsules and oral pellets) are substitutable and product strengths (200 mcg, 400 mcg, 600 mcg, and 1200 mcg) (b) (4) (see Appendix E). (b) (4) We recommend (b) (4) Table 1, and revise as below:

Table 1. Recommended Dosage for 40 mcg/kg/day

Body Weight (kg)	Total Daily Dose (mcg)
7.4 and below	200
7.5 to 12.4	400
12.5 to 17.4	600
17.5 to (b) (4)	800
(b) (4)	(b) (4)
25.5 to 35.4	1200
35.5 to 45.4	1600
45.5 to 55.4	2000
55.5 and above	2400

    e. The statement, (b) (4) We recommend that you consider deleting the statement.

f. Multiple repetitive statements are found throughout Section 2. Delete duplicative statements to streamline the dosing information and increase readability. For example:

1. It is reasonable to expect that healthcare providers will understand how to increase a dose based on set increments (i.e. in 40 mcg/kg increments) therefore delete the bullet stating, (b) (4) [redacted]

2. The applicant has confirmed that both dosage forms (capsules and oral pellets) are substitutable and product strengths (200 mcg, 400 mcg, 600 mcg, and 1200 mcg) [redacted] (b) (4) (b) (4) Therefore, delete the statement (b) (4) [redacted]

3. Full Prescribing Information: 2.2 Preparation and Administration Instructions

a. Recommendations are noted in tracked changes below and made to improve clarity and readability of important preparation and administration instructions:

2.2 Preparation and Administration Instructions

- For patients taking bile acid binding resins, take BYLVAY at least 4 hours before or 4 hours after taking a bile acid binding resin *[see Drug Interactions (7.1)]*.

(b) (4) **Oral Pellets:**

- (b) (4) Mix the contents of the oral pellet(s) (b) (4) into soft food. **Do not mix BYLVAY in liquids.** (b) (4)
- (b) (4) (b) (4) Do not swallow oral pellets whole.
- Patients who are exclusively on (b) (4) liquid food (b) (4) should not use BYLVAY.

(b) (4) [redacted]

(b) (4)

Administration Instructions:

1. Take in the morning with (b) (4) a meal. (b) (4)
2. Place a small amount of soft food (up to 30 mL [2 tablespoons] of apple sauce, oatmeal, banana or carrot puree, chocolate (b) (4) or rice pudding) in a bowl. Keep food at or below room temperature.
3. Open the oral pellet(s) and (b) (4) (b) (4) empty the contents (b) (4) into the bowl of soft food. Gently tap the oral pellet (b) (4) shell to ensure that all contents (b) (4) have been dispersed (b) (4)
4. If the dose requires more than one (b) (4) ~~of~~ oO~~O~~ral p~~P~~ellet~~s~~, repeat step 2 (b) (4) (b) (4)

~~5.~~ Gently mix until well dispersed and (b) (4)

5. a~~A~~dminister the entire dose immediately (b) (4)
6. Follow the dose with water.
7. Do not store mixture for future use.

(b) (4)

(b) (4) **Capsules:**

(b) (4)

Administration Instructions:

1. Take in the morning with (b) (4) a meal.
2. Swallow the capsule whole with a glass of water. (b) (4)

~~3.~~ Alternatively, f~~F~~or patients unable to swallow the capsules whole, BYLVAY (b) (4) (b) (4) capsules may be~~,~~ sprinkled and mixed with (b) (4) a small amount of soft food. Follow directions above for oral pellets to prepare and administer such a mixture. (b) (4)

3.

4. Full Prescribing Information: Section 2.3 Dose Modifications for Management of Adverse Events

    a. Important dose modification instructions are omitted. The statement, (b) (4)

5. Full Prescribing Information: Section 3 Dosage Forms and Strengths

a. The size of the oral pellets and capsules are stated in this section. We defer to Office of Pharmaceutical Quality (OPQ) for appropriateness of including this information in Section 3.

6. Full Prescribing Information: Section 17 Patient Counseling
   a. Critical information regarding the preparation of Bylvay oral pellets or capsule lacks prominence. The statement, "Do not mix Bylvay with liquids" may be overlooked. We recommend bolding the critical statement, "Do not mix Bylvay with liquids".

B. BYLVAY INSTRUCTIONS FOR USE (IFU)

1. Important Information You Need to Know Before Taking BYLVAY (b) (4)
   a. Critical information regarding the preparation of Bylvay oral pellets or capsule lacks prominence. The statement, "Do not mix Bylvay (b) (4) liquids" may be overlooked since it is located as a third bullet point, additionally we note that the liquids are not clearly defined. We recommend presenting this critical information as part of the first bullet, defining the liquids, and bolding the statement to increase readability and prominence.

   - (b) (4) the morning (b) (4) meal. **Do not mix BYLVAY in liquids like breast milk, formula or water.**
   - (b) (4)
   - If (b) (4) taking bile acid binding resins, (b) (4) BYLVAY at least 4 hours before or 4 hours after (b) (4) a bile acid binding resin.

2. (b) (4) Bylvay Oral Pellets
   a. The statement, (b) (4) is confusing. (b) (4) Alternatively, delete the statement as it is duplicative.

3. Taking Bylvay Capsules
   a. This section is presented before (b) (4) Bylvay Oral Pellets", which is inconsistent with the presentation in the PI. We recommend to align the format with the Prescribing Information (PI).

4.2 RECOMMENDATIONS FOR ALBIREO

Identified Issues and Recommendations for Albireo(entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	As currently presented, for the 1,2000 mcg and 600 mcg strengths the products proprietary name (Bylvay) and established name (odevixibat) respectively are presented in the same color scheme as their respective strength statement.	The use of the same color font for the proprietary name and/or established name and products strengths minimize the difference between the strengths, which may lead to wrong strength selection errors.	Revise the font color of the proprietary name (b) (4) and established name (b) (4) or revise the color scheme of the 1,200 mg strength (b) (4) and the 600 mcg strength (b) (4) so that either the strength or the proprietary name and established name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.
2.	The strength statement, 1200 mcg, is presented without a comma.	The reader may misinterpret 1200 mcg as hundreds “120” or ten-thousands “12000”.	Utilize a comma in the presentation of the numeric for the 1200 mcg strength statement. For example, 1,200 mcg
3.	Dosage form statement (b) (4) located on the principal display panels and side panels for the 200 mcg and 600 mcg strengths is inconsistent with the prescribing information (PI).	Inconsistencies between PI and label and labeling may lead to misinterpretation and medication preparation and administration errors.	Revise the dosage form (b) (4) on the principal display panels and on the side panels for the 200 mcg and 600 mcg strengths to be consistent with the PI. For example: oral pellets
4.	The net quantity statement is overly prominent and takes the reader’s attention away from more important product information, such as the proprietary	Post-marketing experience shows that the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is prominent.	Decrease the prominence of net quantity statement and relocate to a less prominent position on the PDP.

Identified Issues and Recommendations for Albireo(entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	name, established name, and product strength.		
5.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
6.	The dosage statement terminology is inconsistent with that used in the Prescribing Information.	21 CFR 201.55	Revise the dosage statement to read, "Recommended Dosage: See prescribing information." on the side panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Bylvay that Albireo submitted on December 22, 2020.

Table 2. Relevant Product Information for Bylvay	
Initial Approval Date	N/A
Active Ingredient	odevixibat
Indication	Treatment of pruritus in patients with progressive familial intrahepatic cholestasis. (b) (4)
Route of Administration	oral
Dosage Form	capsules
Strength	(b) (4): 400 mcg, 1,200 mcg (b) (4): 200 mcg, 600 mcg
Dose and Frequency	The recommended dose is (b) (4) mcg/kg once daily in the morning with a meal. (b) (4)
How Supplied	Bottles of 30
Storage	Store at 20ºC to 25ºC (68ºF to 77ºF); excursions permitted between 15ºC and 30ºC (between 59ºF and 86ºF) [See USP Controlled Room Temperature].

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APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Bylvay labels and labeling submitted by Albireo.

- Container label(s) received on December 22, 2020
- Carton labeling received on December 22, 2020
- Prescribing Information (Image not shown) received on December 22, 2020 \\CDSESUB1\evsprod\nda215498\0004\m1\us\114-labeling\114a-draft-label\proposed.docx

F.2 Label and Labeling Images

Container labels

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[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 17, 2020
To:	Ayanna Augustus Bryant, CPMS Regulatory Project Manager **Division of Hepatology and Nutrition (DHN)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon Williams, MSN, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Meeta Patel, Pharm.D. Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Instructions for Use (IFU)
Drug Names (established names):	BYLVAY (odevixibat)
Dosage Form and Route:	capsules, for oral use oral pellets
Application Type/Number:	NDA 215498
Applicant:	Albireo AB

1 INTRODUCTION

On November 20, 2020, Albireo AB submitted for the Agency's review an original initial New Drug Application (NDA) for odevixibat, a small molecule and a potent selective inhibitor of the ileal bile acid transporter (IBAT), for the treatment of pruritis in patients with progressive familial intrahepatic cholestasis (PFIC).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hepatology and Nutrition (DHN) on April 21, 2021 for DMPP and OPDP to review the Applicant's proposed IFU for BYLVAY (odevixibat) capsules, for oral use and oral pellets.

2 MATERIAL REVIEWED

- Draft BYLVAY (odevixibat) IFU received on November 20, 2020, and received by DMPP and OPDP on May 12, 2021.
- Draft BYLVAY (odevixibat) Prescribing Information (PI) received on November 20, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 12, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 13, 2021

To: Ayanna Augustus, Regulatory Project Manager

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader (OPDP)

Subject: OPDP Labeling Comments for BYLVAY (odevixibat) capsules, for oral use

NDA: 215498

In response to the consult requests dated January 13, 2021 and April 21, 2021, OPDP has reviewed the proposed product labeling (PI) and Instructions for Use (IFU) for the original NDA submission for Bylvay.

Labeling: OPDP has no comments on the proposed labeling based on the draft PI received by electronic mail on May 12, 2021.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed IFU will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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Division of Neurology 1 Consult Memorandum

NDA	**215498**
Applicant:	**Albireo AB**
Drug:	**Odevixibat**
Proposed Indication:	**Pruritus in patients with progressive familial intrahepatic cholestasis (PFIC)**
Material Submitted:	**NDA**
Consult Request Date:	**2/27/21**
Requested Completion Date:	**5/1/21**
Date Review Completed:	**4/29/21**
Clinical Reviewer/Team Leader:	**Emily R. Freilich, M.D.**

The Division of Hepatology and Nutrition (DHN) requested a consult from DN1 regarding appropriate tools and duration for assessing neurocognitive outcomes in young children if DHN requires a postmarket safety study to assess growth and neurocognitive development in PFIC patients taking odevixibat long-term. The consult specifically asked the following questions:

> **We are discussing postmarket safety studies to assess growth and neurocognitive development in PFIC patients taking odevixibat long-term, recognizing that these patients are already at risk due to underlying cholestatic liver disease and concomitant fat-soluble vitamin and nutrient deficiencies. Provide recommendations for assessing these outcomes in postmarket safety studies.**
>
> **Provide recommendations for the following:**
>
> 1. **What are acceptable tools for assessing neurocognitive outcomes children 0 months to 5 years of age?**
> 2. **What would be the appropriate duration over which these neurocognitive assessments should be performed to detect a clinically meaningful change?**
> 3. **What elements (at a protocol level) are critical in a PMR protocol, that would assess neurocognitive outcomes in children <5 years of age?**

Background:

Odevixibat is a new molecular entity proposed for the indication of "treatment of pruritus in patients with Progressive Familial Intrahepatic Cholestasis (PFIC) (b) (4) This is a 505(b)(1) NDA application for a small molecule, submitted by the Applicant, Albireo AB. PFIC is a rare, cholestatic liver disease affecting children (see more information below).

The Applicant conducted a single Phase 3, double-blind, placebo-controlled study of 62 patients with PFIC randomized 1:1:1 to receive odevixibat 40 µg/kg/day, odevixibat 120 µg /kg/day, or placebo for 24-week duration. The primary endpoint in the Phase 3 study was the proportion of positive pruritus assessments at the patient level over the 24-week treatment period. The proportion of positive pruritus assessments for morning and evening scores combined at the patient level was assessed using the Albireo Observer Reported Outcome (ObsRO) instrument.

Patients were rolled over from the double-blind, placebo-controlled trial prematurely into an open-label safety extension study, limiting the assessment of safety over the 24-week period. Neurocognitive outcomes were not assessed in the pivotal study or the long-term extension study. The primary review team is concerned that there are potential near-term and long-term consequences of reducing the intestinal bile acid pool, in a population of patients in which the intestinal bile acid pool is already small, which may lead to reduction in absorption of fat-soluble vitamins, as well as fat. Furthermore, diarrhea is a common adverse event, which could also lead to malabsorption. The potential adverse consequences of fat and fat-soluble vitamin deficiency include poor growth, visual impairment, rickets, and poor neurocognitive outcomes.

Progressive Familial Intrahepatic Cholestasis (PFIC) :

PFIC is a heterogenous group of autosomal recessive genetic disorders associated with chronic cholestasis due to impaired bile acid secretion and transport. In general, disruptions in different abnormal ATP-blinding cassette transporters may disrupt the export of phospholipids and bile flow, leading to chronic cholestasis of varying degrees of severity, and may result in progressive liver fibrosis, cirrhosis, and end stage liver disease. PFIC is typically characterized by early onset of cholestasis (typically infancy or early childhood) with associated pruritus, jaundice, and malabsorption. PFIC is a rare disease, with an estimated incidence of 1:50-100,000, and total number of cases reported in the literature numbering less than 250, and is categorized into 3 main subtypes based on identified genetic mutation. In PFIC-1 and PFIC-2, bile acid secretion is depleted, and in PFIC-3, bile phospholipid secretion is impaired. Of note, patients with PFIC types 1 and 2 may also manifest signs of fat malabsorption, including poor growth and symptoms of fat-soluble vitamin deficiency.

Odevixibat

The Applicant is developing odevixibat for the treatment of pruritus associated with PFIC. Odevixibat is a small molecule that selectively inhibits the ileal bile acid transporter (IBAT) in the distal ileum, without affecting other bile acid transporters. It is intended to act locally in the distal ileum to bind reversibly to IBAT, decreasing the reuptake of bile acids, thereby increasing the clearance of bile acids, lowering the overall hepatic bile acid load, and leading to improvement in cholestasis and associated pruritus. The Division notes that as an inhibitor of IBAT, the drug will substantially reduce the bile acid pool with increased excretion of bile acids in stool, and is concerned that patients receiving the treatment may be at risk for worsening of pre-existing fat and fat-soluble vitamin malabsorption.

Neurocognitive Development and ability to distinguish disease from drug:

The theoretical concern is that further reduction of the bile acid intestinal pool may exacerbate pre-existing fat-soluble vitamin deficiencies (Vitamins A, D, E, and K). Deficiency of fat-soluble vitamins may lead to a variety of symptoms, including night blindness, growth failure, xerophthalmia, leukopenia, rickets, electrolyte disturbances, bleeding, and poor cognitive outcomes. However, patients with PFIC are already at risk for fat-soluble vitamin deficiencies due to their underlying liver disease and malabsorption. It would be challenging to differentiate neurodevelopmental and cognitive delays due to the underlying liver disease from the theoretical worsening due to the treatment itself. However, it also seems as if any treatment-associated worsening of neurodevelopment and cognition would be inherently linked to a

treatment-associated worsening of other fat-soluble vitamin deficiencies, as well as other objective measures, such as growth parameters (e.g., height, weight, BMI).

Assessments of Neurocognition:

Long-term safety outcomes in neurodevelopment, especially cognition, are challenging to assess, especially in this heterogenous patient population, who are already at risk for poor neurocognitive outcomes due to their underlying disease. The ability to detect a safety signal and determine if potential neurocognitive decline is due to treatment compared to the underlying condition would likely require a much larger sample size than is feasible in this very rare condition. The patients in the pivotal study population have already been rolled over into an open-label extension study, so it would be difficult to adequately interpret any uncontrolled neurodevelopmental assessments done as part of a long-term follow-up study. These patients did not have any baseline neurodevelopmental assessments, so comparisons to the patient's own baseline is also not feasible. Similarly, it would be challenging to require a PMR to assess neurocognitive outcomes in such a heterogenous and rare disease that could potentially yield interpretable results.

However, it can be reasonably assumed that the risk to neurodevelopment from treatment with odevixibat would be secondary to an associated risk in other downstream effects of malabsorption and FSV deficiencies. Therefore, if possible, it would appear reasonable to assess long-term safety of the available patients on objective changes in growth and vitamin deficiencies, either in the form of the open-label extension studies, patient registries, or a PMR. If growth is being adversely affected by the treatment, or there are reports of worsening fat-soluble vitamin deficiencies, it can be considered that the treatment would also put patients at higher risk for having an impact on neurocognitive outcomes.

If neurodevelopmental assessments are still being considered in long-term studies, baseline assessments should be obtained when possible, and outcomes should be measured after a minimum duration of 2 years, and longer if concerned about impacts on IQ and executive function. At least one evaluation after a child has reached school age (> 5 years) would also be helpful. The COA Division should be consulted for selection of the appropriate outcome measures, which may vary based on the age and baseline developmental status of the children both at baseline and at the time of follow-up.

Reviewer Conclusions:

This reviewer concludes that it would be very challenging to demonstrate an impact of treatment on neurocognitive outcomes, especially in this small, heterogenous patient population that is already considered high risk for neurodevelopmental delays secondary to their underlying condition, and without any available baseline assessments. An uncontrolled, long-term follow-up study would not be adequate to detect a safety signal for cognition or development in this patient population.

However, this reviewer also notes that the risk for a neurocognitive deficit from the treatment is theoretical, and appears to be based on a perceived increased risk for fat-soluble vitamin deficiency and malabsorption. It is also notable that patients with PFIC are already at risk for fat-soluble vitamin deficiency and poor cognitive outcomes without receiving treatment with odevixibat. It appears reasonable that any treatment-associated worsening of cognitive outcomes and/or neurodevelopment would be associated with other significant adverse event findings of vitamin deficiency, including poor growth, and

watery diarrhea, or evidence of other vitamin deficiencies such as rickets, osteoporosis, etc. Although such adverse events were not noted in the pivotal study, it may not have been long enough to see an effect, especially on growth measures.
If any long-term follow-up studies are required of the Applicant through extension studies, registries, or a postmarketing commitment, it appears that if patients are closely monitored for serious adverse events, nutritional status, and growth outcomes, then additional neurocognitive testing would not contribute significantly to the overall findings of long-term safety of odevixibat in patients with PFIC. Any impact on neurodevelopment could be taken in the context of impact on these other factors.

These conclusions were communicated to the team at the PMR/PMC team discussion on April 16,2020. It appears that other members of the review team were in agreement, and that no neurodevelopmental PMR was going to be issued. Thus, the specific questions raised in the original consult are no longer relevant. If further questions arise, please let us know.

References:

APPEARS THIS WAY ON ORIGINAL

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/s/

EMILY R FREILICH
05/04/2021 10:02:29 AM

TERESA J BURACCHIO
05/04/2021 10:04:12 AM

M E M O R A N D U M

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: May 3, 2021

To: Joseph Toerner, MD, MPH, Director
Division of Hepatology and Nutrition (DHN)

Through: Dominic Chiapperino, PhD, Director
Joshua Lloyd, MD, Medical Officer Team Leader
Controlled Substance Staff (CSS)

From: Silvia N. Calderon, PhD, Senior Pharmacologist
Controlled Substance Staff

Subject: **Product:** Odevixibat (also known as A4250), Tradename, Bylvay
Dosages: (b) (4): 400 mcg and 1200 mcg; (b) (4): 200 mcg and 600 mcg
Recommended Dose: (b) (4) mcg/kg once daily in the morning with a meal
NDA Number: 215498, product developed under IND 130591
Indication(s): Treatment of pruritus in patients with progressive familial intrahepatic cholestasis (PFIC)
Applicant: Albireo AB/Albireo Pharma, Inc.
PDUFA Goal Date: July 20, 2021

Materials Reviewed:

- Abuse-related preclinical and clinical data in NDA 215498 submission, (Sequence 0001, 11-20-2020)

Table of Contents

I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request by the Division of Hepatology and Nutrition (DHN) dated February 16, 2021, to the Controlled Substance Staff (CSS), to evaluate preclinical and clinical data submitted by Albireo AB/Albireo Pharma, Inc (referred to as "the Applicant") for Bylvay (odevixibat capsules) in NDA 215498. Odevixibat capsules were developed under IND 130591. Odevixibat (also known by the development code A4250) is an ileal bile acid transporter inhibitor (IBAT) indicated for the treatment of pruritus in patients with progressive familial intrahepatic cholestasis. Pruritis is a symptom of cholestatic liver disease that may result in biliary diversion surgery and/or liver transplantation in severe refractory cases. The recommended dose is (b) (4) mcg/kg once daily in the morning with a meal. The product will be available in 400 mcg and 1200 mcg (b) (4) and in 200 mcg and 600 mcg (b) (4).

Odevixibat is a new molecular entity not controlled under the Controlled Substances Act (CSA). It has limited oral absorption, is not chemically or pharmacologically similar to other drugs of abuse, and does not interact with receptor sites associated with the site of action of drugs known to be abused.

CSS has not been consulted before on this drug. The Applicant's proposed labeling does not include a Section 9- Drug Abuse and Dependence.

2. Conclusions

1. The available nonclinical and clinical data indicate that odevixibat does not have abuse potential.
2. Odevixibat acts locally in the intestines and is a potent inhibitor of the human ileal acid transporter (IBAT), a sodium and bile acid cotransporter that returns bile acids back to the liver as part of the enterohepatic circulation.
3. Odevixibat is a new molecular entity that has poor oral absorption and it is not chemically or pharmacologically similar to drugs known to be abused.

4. Odevixibat does not have central nervous system (CNS) activity when taken orally, as poor oral absorption results in low drug plasma levels. However, odevixibat reaches the CNS when injected. These conclusions are supported by a quantitative whole autoradiography study performed in rats that demonstrated that odevixibat reaches the brain following intravenous administration. A similar study confirmed that the distribution of orally administered odevixibat was confined to the gastrointestinal tract.
5. An evaluation of binding (Study 25882) demonstrated that odevixibat is a selective inhibitor of the human IBAT and that it did not bind to receptor systems associated with the site of action of drugs of abuse.
6. Behavioral and observational studies conducted in rats (Irwin test, motor coordination study, and spontaneous locomotor activity) demonstrated that, at human equivalent therapeutic and supratherapeutic doses, odevixibat did not have neurobehavioral effects, did not induce motor incoordination, and did not have an effect in locomotor activity.
7. Pharmacokinetic studies confirmed that systemic absorption of orally administered odevixibat was minimal.
8. No abuse-related adverse events (e.g., euphoria, feeling high) were reported in healthy volunteers enrolled in pharmacokinetic studies at doses at which quantifiable levels, though low, of odevixibat were observed. The majority of the adverse events were reported under the GI System Disorders SOC (e.g., abdominal pain, nausea, diarrhea, abdominal cramping).
9. The proposed labeling does not include a Section 9- Drug Abuse and Dependence.

3. Recommendations

Based on our findings described in the Conclusions section:

We agree with the Applicant to not include a Section 9- Drug Abuse and Dependence in the labeling.

II. DISCUSSION

1. Chemistry

The following sections summarize data provided under Module 3-Quality, Modules 3.2.S (Drug Substance) and 3.2.P (Drug Product).

1.1 Substance Information

Odevixibat drug substance is a new molecular entity active pharmaceutical ingredient (API) present in the product as the sesquihydrate form (i.e., 1.5 molecules of water per molecule of odevixibat). It

is known by the chemical name of (2*S*)-2-[[(2*R*)-2-[[2-[[3,3-dibutyl-2,3,4,5-tetrahydro-7-(methylthio)-1,1-dioxido-5-phenyl-1,2,5-benzothiadiazepin-8-yl]oxy]acetyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-butanoic acid sesquidrate; by the code names A4250, AZD8294, AR-H064074, and (b) (4); and by (b) (4). The Chemical Abstract number is 501692-44-0 for the anhydrous form and 2409081-01-0 for the hydrate form. The molecular formula is $C_{37}H_{48}N_4O_8S_2$ for the anhydrous form and $C_{37}H_{48}N_4O_8S_2$. 1.5 H_2O for the hydrate form. Molecular weights are 740.9 g/mol (anhydrous form) and 768.0 g/mol (sesquihydrate form).

The drug substance has two chiral centers; however, the configuration at both chiral centers is fixed. Thus, it is available as one stereoisomer with the *S* and *R* configuration as shown if **Figure 1**.

Odevixibat is not chemically similar to drugs known to be abused (e.g., benzodiazepines, opioids).

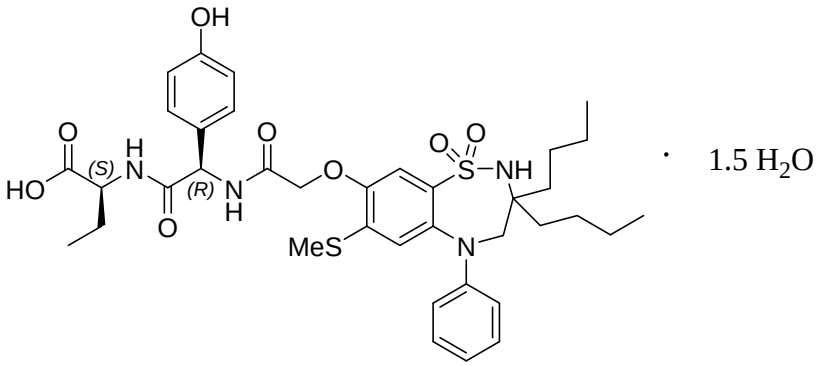

Figure 1: Chemical structure of odevixibat sesquihydrate

The API is described as a white to off white solid with a melting point of 133.7 °C. The solubility of the API is pH dependent, and it was found to be insoluble in aqueous buffers pH 1 to 4.

The aqueous solubility at 24 hours, measured at 37 °C, is 10.30 µg/mL at pH 7 and 8.72 µg/mL at pH 8.0. LogD values for odevixibat at different pH (**Table 1**) show that the lipophilicity of odevixibat decreases with pH. Thus, membrane permeability will be higher at lower pH values.

Table 1: Partition Coefficient for odevixibat, Log D at various pH (This table is based on the Applicant's Table 1 presented in Module 3.2.S.1.3 General Properties)

pH	Method	Value
1.0	HPLC	5.2
5.0	Shake Flask	>3.68
6.0		3.46
7.0		2.99
8.0		2.78

The manufacturing process of the drug substance is described in Module 3.2.S.2.2 and (b) (4)

1.3 Drug Product

The drug product will be available in four different strengths (200 µg, 400 µg, 600 µg and 1200 µg) The 400 µg and 1200 µg capsules are intended for direct oral administration, whereas the 200 µg and 600 µg capsules are intended to be sprinkled over food. (b) (4)

(b) (4)

2. Nonclinical Pharmacology

Odevixabat is a potent inhibitor of the human ileal acid transporter (IBAT), which is a sodium and bile acid cotransporter that returns bile acids back to the liver as part of the enterohepatic circulation. The Applicant states that the transporter is expressed mainly in the distal ileum of several species, including mouse, rat, rabbit, dog, monkey, and human. Odevixibat acts locally in the gut, with minimal systemic exposure, and binds to the IBAT to decrease the reuptake of bile acids, thus increasing their clearance from the body. The low permeability of odevixibat across the intestinal epithelium it is expected to result in low plasma levels of the drug.

2.1 Receptor Binding and Functional Assays

An evaluation of binding (Study 25882) demonstrated that odevixibat is a selective inhibitor of the human IBAT. Binding of odevixibat to a panel of 5 enzymes (acetylcholinesterase, cyclooxygenase COX1, monoaminoxidase, protein/serine/threonine kinase, ERK2 proteins) and 12 receptors (alpha-1 adrenergic, alpha- 2 adrenergic, beta-1 adrenergic, norepinephrine transporter, dopamine D2, alpha estrogen, GABAA, histamine H1, Muscarinic M2, nicotinic/acetylcholine, opioid mu, and serotonin 5 HT2A) demonstrated that, at 1 µM concentration, odevixibat did not bind to the enzymes or receptors tested.

2.2 Findings from CNS Safety Pharmacology and Toxicology Studies

The following sections provide a brief overview of study results for the various relevant studies conducted by the Applicant, as reported in the corresponding study reports (Module 4.2.1.2- Secondary Pharmacodynamics and Module 4.2.1.3- Safety Pharmacology).

Safety pharmacology and toxicology studies were conducted in rats, as this species is considered predictive of the pharmacology in humans.

- *Absorption and metabolism in animals*

Odevixibat is poorly absorbed orally and is highly protein bound (≥ 99.2 %) in mouse, rat, dog, marmoset, and human plasma. Odevixibat has very low oral bioavailability and its excreted predominantly unchanged in feces.

A quantitative whole body autoradiography study (Study 00667PR) performed in male rats (Han Wistar, Long Evans black hooded) demonstrated that, following a single oral dose of [^{14}C]odevixibat (3.7 mg/kg), the absorption of [^{14}C]odevixibat was low, as levels of unchanged parent drug or its metabolites, or both, were found confined to the gastrointestinal tract, gastric mucosa, wall of small intestine, bile, kidney cortex, liver, prostate gland, and skin. Following intravenous administration of 1.85 mg/kg of [^{14}C]odevixibat to rats, radioactivity was rapidly distributed throughout the body, including the CNS, and almost all radioactivity was eliminated via bile. These data demonstrate that the drug crosses the blood brain barrier if administered intravenously and that the poor oral absorption of the drug limits the amount of drug present in plasma and consequently the amount of drug that reaches the brain.

The metabolism of [^{14}C]odevixibat was determined in vitro, using hepatocytes from rat, dog and human, and in vivo following oral administration of 3 mg of odevixibat to healthy human volunteers (Study A4250-007). In humans, 83% of the dose was excreted in feces. No active metabolites were identified in animals or humans.

- *Irwin test and effect on body temperature (Study 20040104PGR)*

Study animals were observed for neurobehavioral effects using a standard observational battery of tests to assess the CNS effects of the test drugs (e.g., motor activity, behavior, coordination, somatic sensory motor/reflex responses and autonomic responses such as pupil size, piloerection, lacrimation, salivation, and overt cardiovascular and gastrointestinal effects). The effect of odevixibat on body temperature was also assessed.

The study was conducted in Wistar male rats under fed conditions, and the test drug was orally administered at doses of 1 µmol/kg, 10 µmol/kg, and 100 µmol/kg.[1] The control group received chlorpromazine at a dose of 20 mg/kg, and the placebo group received sodium bicarbonate buffer solution 10 µmol/mL, pH 9.5. (Note: The study report states that odevixibat was administered in the order of moles/kg dose. However, considering the molecular weight of odevixibat hydrate (768 g/mol or 768 µg/µmol), this reviewer considers that, similar to the dosing used in other behavioral studies, the g/kg dosing represents a typo and that instead animals received µmol/kg doses.

[1] Considering that a µmol of odevixibat weighs 768 µg (0.768 mg) and that the conversion factor to convert a mg/kg dose tested in rats to a human equivalent dose is 6.2, a 1µmol/kg rat dose would be equivalent to a 123 µg/kg human dose (768 µg/kg / 6.2= 123 µg/kg), which is in the recommended therapeutic dose range (120 µg/kg). Doses of 10 µmol/kg and 100 µmol/kg are considered supratherapeutic doses (10.3 and 103 times the recommended therapeutic dose, respectively). For conversion factors, see the 2015 FDA Guidance for Industry- Estimating the Maximum Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers at https://www fda.gov/media/72309/download.

Irwin scores and body temperature measurements were performed at 1, 2, 4, 6, and 24 hours after drug administration. Observers were not aware of the treatment each animal received. Under the experimental conditions of the study, the Applicant reports that no adverse neurobehavioral effect at any dose tested was observed. Under the same conditions, sedative, myorelaxant, and hypothermic effects were observed upon oral administration of chlorpromazine at 20 mg/kg, confirming validity of the conditions selected.

- *Motor Coordination (Study 20040103PGR)*

The effects of odevixibat on motor coordination were measured in the rotarod test following oral administration of 1 μmol/kg, 10 μmol/kg, and 100 μmol/kg doses, in Wistar male rats and under fed conditions. Chlorpromazine 10 mg/kg served as the positive control.[1] Two days prior to the study, animals were trained on a rod rotating at 5 revolutions per minute, and, on the day of the study, animals were selected based on their ability to remain on the rod rotating at 20 revolutions per minute for at least 1 minute. Upon receiving the test drug, positive control or placebo, measures were taken at 1, 2, 4, 6, and 24 hours after drug administration. The study conditions were validated by the positive control, which, at the tested doses, induced marked motor incoordination. Odevixibat, at the doses tested, did not have an effect on motor coordination.

- *Spontaneous Locomotor Activity (Study 20040102PGR)*

The effects of odevixibat on spontaneous locomotor activity were evaluated in male Wistar rats under fed conditions and following single oral doses of 1 μmol/kg, 10 μmol/kg, and 100 μmol/kg. Chlorpromazine was used as the positive control at a dose of 20 mg/kg. Upon drug administration, animals were placed individually into an open field arena at 1, 2, 6, and 30 hours after dosing. Locomotor activity, exploratory behavior, and stereotypies were assessed by measuring motor activity and rearing in peripheral and central zones, grooming, and duration of immobility for the 10 -minute period following placing the animal in the arena. Observations were performed using a video monitor.

Under the conditions of the study, odevixibat did not have effects on locomotor activity at 1, 2, 6, or 30 hours following oral administration of the 1 μmol/kg dose. Although effects were not observed at 1, 2, or 6 hours for the 10 μmol/kg and 100 μmol/kg doses, a delayed slight decrease in locomotor activity was observed at 30 hours postdosing in these dose groups. These findings are hard to explain because no active metabolites of odevixibat have been identified. A decrease in spontaneous locomotor activity and in exploratory behavior was observed at 1 hour following the administration of chlorpromazine, validating the study.

- *General toxicology findings (Module 2.4, Common Technical Document Summaries, Nonclinical Overview)*

The Applicant states that odevixibat was well-tolerated upon single oral administration in the 1-month study in rat (Study 0664AR) and repeat oral administration across rodent [mouse (Study TEA0013) and rat (Study TEA0001)] and non-rodent species [dog (Study 9348308) and marmoset (Study 0011DT)]. Drug-related target organ toxicity included the gastrointestinal tact (mouse, rat and dog), gallbladder (mouse), kidney (rat), parotid gland acinar cell (rat), cardiovascular system

(embryo fetal rabbit), and liver (adult general rats). The Applicant concluded that, "*following both single and repeat administration, clinical symptomatology was primarily GI, with associated reductions in body weight and/or food consumption.*" No potential CNS toxicity was observed in toxicology studies.

2.3 Tolerance and Physical Dependence Studies in Animals

Physical dependence and tolerance studies were not conducted.

3. Clinical Pharmacology

This section summarizes key clinical pharmacology findings, as described by the Applicant in Module 2.5 Clinical Overview and Module 2.7.2 Summary of Clinical Pharmacology Studies.

- *Absorption, Distribution, Metabolism, Elimination (ADME)*

An ADME study (Study A4250-007) in healthy volunteers showed that, following a single oral dose of 3 mg of [^{14}C]odevixibat, 83% of the total radioactivity was recovered in feces and an average of 0.002% in urine. Higher than 97% of the fecal radioactivity was determined to be unchanged odevixibat, suggesting minimal metabolism. This study also showed that there was no quantifiable concentration of odevixibat in plasma or total radioactivity in plasma or in whole blood indicating low bioavailability.

In human hepatocytes, odevixibat was minimally metabolized, and the few metabolites identified were mainly mono-hydroxy compounds.

Binding of odevixibat to human plasma proteins was higher than 99.7% determined by equilibrium dialysis at actual concentrations of 4 μM and 40 μM following incubation at 37 °C for 2 hours.

4. Clinical Studies

This section provides an overview of the human pharmacokinetic (PK) data collected by the Applicant upon single and multiple ascending dose administration (SAD/MAD).

The Applicant conducted three Phase 1 studies in healthy volunteers: Study A4250-001 (SAD/MAD study); Study A4250-004 (food effect study); and Study 4250-013 (drug interaction study).

The PK data from these Phase 1 studies confirmed that systemic absorption following oral administration of odevixibat was minimal.

- *Study A4250-001*

Study A4250-001 was a two-part, double-blind, placebo-controlled, single and multiple ascending dose evaluation. The goals of the study were: 1) to assess the safety, tolerability, PK, and pharmacodynamics of odevixibat as monotherapy after single oral doses in fasted state subjects (Part 1-single dose) and 2) to evaluate the safety, tolerability, PK, and pharmacodynamics as monotherapy

after multiple oral doses of odevixibat or when given in combination with a cholestyramine release product (colonic release cholestyramine, CRC) or with commercially-available cholestyramine, Questran (Part 2-multiple dose).

Subjects enrolled in Part 1 (39 subjects enrolled and completed the study, 17 males/12 females) received single oral doses of 0.1 mg, 0.3 mg, 1 mg, 3 mg, or 10 mg on Day 1 [2] of the Study following an overnight fast, and remained on site until 24 hours postdose. A follow-up visit was performed at 5 to 7 days after postdose. In Part 1, quantifiable plasma concentrations were seen only at the highest dose of 10 mg. The median time to maximum concentration (Tmax) was 4 hours.

Subjects enrolled in Part 2 (55 subjects enrolled and completed the study, 33 males/22 females) received either 1 mg or 3 mg of odevixibat once-a-day, 1.5.mg odevixibat twice-a-day, or 3 mg of odevixibat combined either with a CRC under development or with a commercially-available cholestyramine product twice-a-day, all for 7 days. Subjects were dose for 7 days with the last dose administered on Day 7, with subjects receiving the last dose in the morning if they were in the group receiving only one dose a day or receiving the last dose in the evening if they were in the twice a day dosing group. In Part 2, absorption was limited, and quantifiable plasma levels were observed at the 3 mg daily dose, either administered as a once daily dose or as a 1.5 mg twice-a-day dose.

- *Study A4250-004*

Study A4250-004 was an open-label, randomized, 3-way crossover food effect and sprinkle on applesauce study conducted in healthy volunteers. The objectives of the study were: 1) to determine the effect of a high fat meal on single-dose odevixibat PK and 2) to determine the effect of odevixibat sprinkled on applesauce on the single-dose PK of odevixibat. The study enrolled 17 subjects (12 males/5 females), 16 of which completed the study. The dose of odevixibat tested was 9.6 mg.[3]

Exposure to the drug was lower in both the fed state and when taken with applesauce, as compared to the fasted state. Following administration of 9.6 mg of odevixibat, the geometric mean maximum plasma concentration (Cmax) values were 0.547 ng/mL (fasted), 0.161 ng/mL (high fat meal), and 0.337 ng/mL (sprinkled on applesauce). Tmax was delayed approximately 1.5 hours when administered after a high fat meal or when sprinkled on applesauce, as compared to administration under fasted conditions (Tmax, fasted, 3-4.5 hours). However, consistent with the low oral bioavailability of odevixibat, plasma concentrations and systemic exposure to odevixibat were low regardless of fed status.

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[2] Six subjects were in the cohort receiving 10 mg of Odevixibat. Their weights ranged from 53.6 kg to 95.7 kg (53.6; 58.9; 59.8; 89.0; 95.5 and 95.7). The dose/kg conversion for these subjects translates to a range of 186 mcg/kg to 104 mcg/kg. If the therapeutic dose is a 120 mcg/kg, some of the subjects received slightly higher doses than the therapeutic dose with some receiving lower doses than the recommended dose.

[3] The weight of the subjects enrolled ranged from 56.8 kg to 99.9 kg, indicating that some of these subjects received doses that were slightly higher than the recommended therapeutic doses and some received doses below the recommended dose.

- *Study A4250-013*

Study A4250-013 was a two-part (Part A and Part B), open-label, fixed sequence, drug-drug interaction study with midazolam and itraconazole. The goals of Part A were to determine the effect of odevixibat on the PK of midazolam (a cytochrome CYP3A4 substrate) and to determine the safety and tolerability of odevixibat when co-administered with midazolam in healthy adult volunteers (22 subjects, 12 males/10 females enrolled, 20 subjects completed this part of the study). The goals of Part B were to determine the effect of itraconazole (a P-glycoprotein inhibitor) on the PK of odevixibat and to determine the safety and tolerability of odevixibat when co-administered with itraconazole in healthy adult volunteers (21subjects were enrolled and completed this part of the study, 6 males/15 females). In Part A, 7.2 mg of odevixibat was administered once daily for 4 consecutive days with midazolam (2 mg) administered on Day 4. In Part B, itraconazole (200 mg) was administered once daily for 5 days and odevixibat (7.2 mg) was administered on Day 5.

Part A of the study demonstrated that once-a-day administration of 7.2 mg of odevixibat decreased exposure to midazolam approximately by 30% and exposure to 1-OH midazolam by less than 20%.

Part B of the study demonstrated that once-a-day administration of itraconazole over a 5-day period increased plasma exposure of a single 7.2 mg dose of odevixibat by approximately 50-60% compared to when odevixibat was taken alone.

The Applicant concluded that, based on the low systemic exposure of odevixibat, the exposure increases observed in Part A and Part B of this study were not clinically relevant. As such, the Applicant concluded that no dose adjustment was necessary for patients taking CYP3A4 substrates or P-gp inhibitors.

4.1 Human Abuse Potential Studies

Human abuse potential studies were not conducted.

4.2 Adverse Event Profile in Clinical Studies

The clinical development program for odevixibat consisted of seven studies, including four Phase 1 studies in healthy adults (Study A4250-001: first -in-human, single and multiple ascending dose study; Study A4250-004: food effect study; Study A4250-007: mass balance recovery, metabolite profile and metabolite identification of [^{14}C]odevixibat, and Study A4250-013: drug-drug interaction study with midazolam and with itraconazole), one Phase 2 study in pediatric patients with cholestatic liver disease (Study A4250-003), and two Phase 3 studies conducted in pediatric patients with PFIC (Studies A4250-005 and A4250-008). Odevixibat was studied in 258 subjects, including 87 patients with progressive familial intrahepatic cholestasis (PFIC) and 10 with other cholestatic liver diseases.

The review of the adverse events reported in the Phase 1 studies conducted in adult healthy volunteers is considered to be most informative for the abuse potential assessment since the Phase 2 and 3 studies were conducted in pediatric populations who are experiencing symptoms from their clinical condition, both of which can limit detection of an abuse potential signal. The review of these data is based on a line review of the data provided in Module 5.3- Clinical Study Reports,

5.3.4.1- Healthy Subject PD and PK/PD study Reports (Study A4250-001),16.2.7 Adverse Event Listing; Module 5.3.3.4 Extrinsic Factor PK Study Reports (Study A4259-004), 16.2.7 Adverse Events Listing; Module 5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports, Clinical Study Report Body; and Module 5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies (Study A4250-013), 16.2.7 Adverse Events.

No abuse-related adverse events were reported in any of the four Phase 1 studies mentioned above (e.g., euphoria, feeling high, etc.). The majority of adverse events (AEs) were reported under GI System Disorders SOC, including abdominal pain, nausea, diarrhea, abdominal cramping. A few AEs of headache were reported under the Nervous System Disorders SOC.

In Phase 2 and 3 trials, the most common adverse events reported were diarrhea, vomiting, and alanine aminotransferase increased.

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Clinical Inspection Summary Report

Date	May 4, 2021
From	Zana Marks, M.D., M.P.H. Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Ruby Mehta, M.D., Clinical Team Leader Yao-Yao Zhu, M.D., Clinical Reviewer Ayanna Augustus Bryant, RPM Division of Hepatology and Nutrition (DHN) Office of New Drugs (OND)
NDA #	215498
Applicant	Albireo Pharma, Inc.
Drug	Odevixibat
NME	Yes
Therapeutic Classification	Ileal bile acid transporter inhibitor
Proposed Indication	Treatment of pruritus in patients with progressive familial intrahepatic cholestasis (PFIC)
Consultation Date	January 14, 2021
Review Priority	Priority
Summary Goal Date	June 1, 2021
Action Goal Date	July 20, 2021
PDUFA Date	July 20, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from study A4250-005 and A4250-008 (an extension study) were submitted to the Agency in support of this New Drug Application (NDA 215498) for the use of odevixibat for the treatment of pruritus in patients with progressive familial intrahepatic cholestasis. The extension study was reviewed for safety only. Study drug approval will be based on the results of Study A4250-005. Two clinical investigators who participated in Study A4250-005 were selected for inspection: Dr. Patrick McKiernan [Site 25111] and Dr. Buket Dalgic [Site 23102] and the sponsor Albireo Pharma, Inc. were inspected.

The inspections found no significant regulatory violations at neither of the two investigator sites nor the sponsor Albireo Pharma, Inc. The Applicant's submitted clinical data listings were verifiable against source records, with no discrepancies identified. The clinical data generated by the inspected investigators appear reliable. Based on the results of these inspections, Study A4250-005 appears to have been conducted adequately, and the clinical

data generated from inspected sites appear to be reliable in support of this NDA.

II. BACKGROUND

Odevixibat (A4250) is a small molecule that acts as a potent, selective inhibitor of the ileal bile acid transporter (IBAT) also known as the apical sodium-dependent bile acid transporter (ASBT). It is being developed to treat progressive familial intrahepatic cholestasis (PFIC), a cholestatic liver disease that is life threatening and is associated with significant morbidity. NDA 215498 was submitted to the agency on November 11, 2020.

The sponsor conducted Study A4250-005 which is a Phase 3, double-blind, randomized, placebo-controlled trial to demonstrate the efficacy and safety of odevixibat in children with progressive familial intrahepatic cholestasis Types 1 and 2 (PEDFIC 1) at doses of 40 µg/kg/day and 120 µg/kg/day administered once a day compared to placebo.

The duration of the study was to include an 8-week Screening Period followed by a 24-week Treatment Period and a 4 -week Follow-Up Period. Screening procedures were to include medical and surgical history, concomitant medications, genetic confirmation for PFIC, physical examination, vital signs, and laboratory assessments, including serum bile acids, hematology, chemistry, coagulation profile, and fat-soluble vitamin levels. At the first visit during screening, patients and/or their caregivers were to be provided an electronic diary (eDiary) to record patient-reported (patients ≥8 years of age) and observer-reported (caregivers for all patients) outcome items from the Albireo Patient-Reported Outcome (PRO) and Observer-Reported Outcome (ObsRO) instruments for evaluation of pruritus (itching and scratching, respectively) and sleep disturbance; data were to be entered twice daily.

After completion of the Screening Period, eligible patients were to be randomized on Day 0 (Visit 3) in a 1:1:1 fashion to receive 40 µg/kg/day or 120 µg/kg/day of odevixibat, or a matching placebo. During the treatment period, patients were to return to the clinic at Weeks 4, 8, 12, 18, 22, and 24 (End of Treatment). Assessments to be conducted on the day of randomization (Day 0) and the on-treatment visits were to include physical examinations, vital signs, laboratory assessments, abdominal ultrasound, quality of life (QoL) assessments (Pediatric Quality of Life questionnaire [PedsQL] and global symptom relief based on the Global Impression of Symptoms (GIS) and Global Impression of Change [GIC] instruments), Fibroscan®, and review of concomitant medications and adverse events (AEs).

Patients who complete the Treatment Period and Visit 9 (Day 168, EOT), were to be invited to participate in a 72-week open-label extension study (A4250-008). All patients were to receive active treatment 120 µg/kg/day of odevixibat. A patient who prematurely withdraws due to no improvement or intolerable symptoms, and who completed at least 12 weeks of the Treatment Period and the End of Treatment Visit, was to be offered the opportunity to enter the extension study as well.

The primary efficacy endpoints for Study A4250-005 were region based. For the US, the primary endpoint was the proportion of positive pruritis assessments at the patient level over the 24-week treatment period, where a positive pruritus assessment was defined as a scratching score of ≤1 or at least a 1-point drop from baseline on the Albireo ObsRO instrument. Both AM and PM pruritus assessments were included in the analysis.

The primary efficacy endpoint of the study in the European and Rest of the World (RoW) (including the selected inspection site in Turkey) was the proportion of patients who experienced at least a 70% reduction in serum bile acids concentration from baseline to the end of treatment or reached a level ≤70 μmol/L (28.6 μg/mL).

A total of 62 subjects were enrolled into Study A4250-005 at 33 study sites in the US, Europe, and the RoW.

These inspections were conducted as part of the routine PDUFA pre-approval clinical investigation data validation in support of NDA 215498 in accordance with Compliance Program 7348.811. Site # 24102 (Buket Dalgic, M.D) and Site # 25111 (Patrick J. McKiernan, M.D) were selected based on the number of study subjects compared to the other study sites. No study site enrolled more than 6 subjects. The sponsor was selected for site inspection because the product (A4250/odevixibat) is a new molecular entity and this application is their first submission to the Agency for marketing approval.

III. RESULTS (by Site)

1. Patrick J. McKiernan, M.D. [Site 25111]

UPMC Children's Hospital of Pittsburgh
4401 Penn Avenue
Faculty Pavillion 6th Floor
Pittsburgh, PA 15224-1334

Dr. McKiernan was inspected on March 15-22, 2021 as a data audit for Study A4250-005. This was the first FDA clinical inspection of the investigator.

Dr. McKiernan consented and screened 4 subjects into Study A4250-005. However only 3 subjects were eligible and were randomized and treated with either the investigational product or placebo, including 2 subjects assigned to A4250 120ug/kg/day and 1 subject assigned to placebo. The three randomized subjects are currently participating in the open-label extension study. All four subjects completed the blinded phase of the study and are now in long term open-label follow-up.

All subjects' source records were reviewed and compared with the Applicant's submitted data listings for the site. The reviewed records included the informed consent forms, inclusion/exclusion criteria, randomization scheme, primary endpoint data, adverse events, protocol deviations, laboratory tests, and electronic case report forms (CRFs). Blinding procedures were reviewed. Regulatory documentation was also

examined, including the Institutional Review Board (IRB) approvals of the study protocol and amendments, signed investigator agreements (Form FDA 1572s), delegation of duties log, financial disclosures, site training records, investigator's reporting to sponsor, monitoring records, and investigational drug storage and accountability records.

The site conducted protocol-required assessments including physical exams, skin assessments, vital signs, height and weight, blood draws and abdominal ultrasound. Inspection verified the following data by comparing the source documents in the study records for Subject #s (b) (6) with listings provided with the background package:

- Demographic details
- Pruritis data for all subjects at all time points
- Adverse event data
- Prior and concomitant medications
- Fasting serum bile acid concentration for Visits 1 and 2 (the fasting sBA concentrations tests were blinded starting with Visit 3).
- Laboratory chemistries i.e., ALT, AST, Albumin, GGT, and Alkaline Phosphatase, INR results, 25-OH Vitamin D, alpha-Tocopheral, Total and Direct Bilirubin, and Vitamin A

No discrepancies were found in comparing source data to line listing data with regards to vital signs, physical examinations, skin assessments, abdominal ultrasound, genetic laboratory testing, and liver biopsy results.

There appeared to be no under-reporting of adverse events.

One protocol deviation was not documented (Deviation ID #121733101) involving Subject (b) (6) at Visit 9. The deviation involves the collection of PK, C4 and Autotaxin blood samples in a patient weighing under 10 kilograms. The deviation for Subject (b) (6) (7.7kg) was not included in the protocol deviation list or in Listing 7, Protocol Deviations.

For Subject (b) (6) (9.47 kg) at Visit 9, there was a deviation that involved the collection of PK, C4 and Autotaxin blood samples in a patient weighing under 10 kilograms that was included in the protocol deviation list.

These deviations were discussed at the close out meeting. Dr. McKiernan was aware of the protocol deviation for Subject (b) (6) but did not report it to the IRB because he felt there was no increased risk to the subject and the amounts collected were within study guidelines, thereby not meeting the IRB's requirements for reporting. While the deviation occurred twice despite protocol training, written reminders and supervision by the study coordinator, Dr. McKiernan indicated that for future studies, they may need to add the specific tubes that need to be collected to the source documents. Also, the study coordinator will provide a verbal reminder to the nurse indicating which

samples to collect. There were no adverse event reports related to the protocol deviation for either subject.

There were no significant regulatory violations in study conduct and no Form FDA 483, Inspectional Observations, was issued to Dr. McKiernan at the conclusion of this inspection.

2. Buket Dalgic, M.D. [Site 23102]
Gazi University
Yasar Bostandi Sokak
Besevlr/Ankara, 06500 Turkey

A remote regulatory assessment (RRA) of Dr. Dalgic regarding her participation in Study A4250-005 was conducted on March 26, 2021-April 12, 2021. An onsite inspection was not possible due to travel restrictions caused by the COVID-19 pandemic. As an alternative, video conferencing via WebEx, document sharing via an online platform (box.com), and read-only access to the online trial master file information were utilized to exchange information. Dr. Dalgic has no prior inspection history with FDA.

Dr. Dalgic screened 13 subjects and enrolled 4 subjects into Study A4250-005 including 1 assigned to A4250 120ug/kg/day and 3 assigned to 40ug/kg/day. All 4 subjects completed the blinded phase of the study and remain in the long term open-label follow-up. All 4 enrolled subject's records were reviewed during RRA.

Documents at the study site were uploaded to Box.com for review and included the following:

- Redacted version of source records for Subjects (b) (6)
- Protocol versions approved and used during the study
- English version templates of Informed Consent
- IP accountability, storage, and shipment records
- Delegation activity log
- Site monitor log
- Curriculum vitae of principal investigator and sub-investigators
- Site procedures established during the COVID-19 pandemic

Reviewer's comment(s): *The review was limited in scope due to the logistical constraints of the information exchange. Ethics committee review and Financial Disclosure were not covered during the assessment. However, the review included the requested records from the site's regulatory files, site activities during the COVID-19 pandemic, translation of source records, interviewing study site personnel, adverse event documentation, subject selection, randomization, and blinding activities of four enrolled subjects, adverse event details, IP accountability and efficacy endpoints.*

Meetings with site staff were held via WebEx conference calls with a translator provided by the sponsor. Procedures at the site including informed consent, maintenance of the study blind, staff training, investigational product control, and data management were reviewed with Dr. Dalgic and site staff.

A close out discussion included following up on shipping records to document that Subject (b) (6) received IP for Visits 5 and 6 at home due to COVID-19 pandemic travel restrictions. Initially, source documents did not contain shipping documentation for verification. However, Dr. Dalgic submitted the shipping records to CDER for review and were attached to the (RRA) memo as Exhibit 18.

For the investigational product, inadequate temperature log records that involved missing entries, lack of signature sign off and use of incorrect initials not documented in the delegation log were discussed with Dr. Dalgic and the site staff. Dr. Dalgic promised to correct this with the study coordinators recording the daily temperature.

The assessment verified that the clinical investigator followed the protocol with respect to subject selection, randomization, blinding, and evaluations based on the laboratory reports included in the subject source files.

There were no discrepancies involving the primary endpoint for the four enrolled subjects at the site. No unreported adverse events were identified. No significant study conduct concerns were identified in this remote regulatory assessment.

3. Albireo Pharma, Inc.
10 Post Office Square, Suite 1000
Boston, MA 02109-4603

Albireo Pharma, Inc. was inspected on February 10-12, 2021 and February 16, 2021. This was the first FDA inspection of this Sponsor. This surveillance inspection covered the responsibilities of Albireo Pharma, Inc. (Albireo) as the sponsor for the study drug A4250 (Odevixibat) as used in Study A4250-005 titled “A Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study to Demonstrate Efficacy and Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 1)”.

The inspector reviewed records that included but were not limited to presentations, organizational charts, contracts, transfer of obligations, standard operating procedures (SOPs), monitoring plans, monitoring reports, qualifications of monitors, laboratory data, eDiary data, test article procedures and documentation, and pharmacovigilance procedures and documentation.

Albireo had written procedures in place for selection and oversight of vendors. (b) (4) was contracted to conduct study management activities. Study management activities included study site monitoring, drug accountability, safety reporting, regulatory submissions, data management, Interactive Web Response System

(IWRS), central lab and specialty lab testing, eDiary, patient travel and reimbursement, and patient recruitment and retention.

The inspection focused on the following two study sites:

1) Study site #25111 Clinical Investigator: Patrick McKiernan, M.D.
2) Study site #24102 Clinical Investigator: Anastasios (Tasso) Grammatikopoulos, M.D.

During the review of records for Sites 25111 and 24102, the inspector noted that 11 subjects had not completed 24 weeks of treatment. These subjects were early rollovers into Study A4250-008 an open label extension study. Prior to the current Protocol Version #6 (6/24/19), subjects who completed 12 weeks of treatment who were then withdrawn from the study due to patient/caregiver judgment of no improvement/intolerable symptoms could enroll in the open-label extension study. These 11 subjects discontinued treatment early due to a reported lack of efficacy. They are discussed in the Clinical Study Report (CSR) Section 10.1; pages 99-100. The provision for early entry into the open label study is no longer a part of the protocol.

Training and site initiation visits (SIV) were conducted. SIV documentation showed the study sites reviewed received training, confirmed qualifications, and informed the study site in regard to all aspects of the study, including the protocol and study procedures.

A review of the monitoring reports for the two study sites reviewed during this inspection found no issues with monitoring. On site monitoring was being conducted within appropriate timeframes. The EDC was reviewed and showed queries made by monitors within the data audits. Monitoring reports indicated the monitors were conducting source data verification and source document review.

Albireo's Quality Assurance unit is a separate entity from the clinical operations. They maintain their own quality procedures.

Serious adverse events were reviewed by comparing the electronic case report forms (eCRFs) to the data listings. There was no evidence of underreporting of serious adverse events. There were no reported 15-Day IND safety reports. The study coordinator confirmed that none of the SAEs were reported late.

The Data Safety Monitoring Board (DSMB) conducted adjudication of liver events and determined if the liver events were related to the study drug. Liver events from the DSMB were compared to liver events documented in the CSR's list of adjudicated liver events. All cases sent to the DSMB for the study reviewed for this inspection were found by the DSMB to not be related to the study drug.

The Electronic Data Capture (EDC) used for this study was Oracle InForm. The electronic case report forms (eCRFs) in were reviewed in PDF format. The eCRFs had audit trails showing who made entries, when they were made, what the entry was, and,

if changed, who made the change, when the change was made, what was changed, and reason for the change. A handheld electronic diary (eDiary) was used by subjects or caregivers to document scratching/itching, which was used for an efficacy endpoint.

The inspector conducted a data audit of the endpoints for pruritis assessments (scratching/itching) and serum bile acid (sBA) levels.

For the pruritis assessment data audit, data files from the electronic diaries were collected. The inspector compared scratching/itching scores from eDiary data and compared them to the data listings. The inspection reviewed all subjects at the two study sites 25111 and 24102 and randomly chose at least 20 scratching/itching scores for review for each subject. All data matched.

For the serum bile acid (sBA) data audit, data files from the central laboratory were collected. Serum bile acid values (sBA) from the laboratory data file were compared with the data listings. All sBA values for each subject at the two study sites were included and reviewed. All data matched.

The electronic clinical outcome assessment (eCOA) platform used for the eDiary was called (b) (4). The eDiary was distributed to the subjects or caregivers at the study site where the study site assisted in setting up the eDiary.

There were no discussion items at the close-out meeting on February 16, 2021. No Form FDA 483, Inspectional Observations, was issued.

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Zana Marks, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Min Lu, M.D., M.P.H.
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cc:

Central Documentation
Review Division /Division Director
Review Division/Medical Officer
Review Division /Medical Team Leader
Review Division /Project Manager
OSI/Office Director
OSI/DCCE/ Division Director
OSI/DCCE/GCPAB Chief
OSI/DCCE/GCPAB Team Leader
OSI/ GCP Program Analysts
OSI/Database Project Manager

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: April 21, 2021

To: Ayanna Augustus, Regulatory Project Manager (DHN)

Joette Meyer, Associate Director for Labeling (DHN)

From: Meeta Patel, Pharm.D., Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kathleen Klemm, Team Leader (OPDP)

Subject: OPDP Labeling Comments for BYLVAY (odevixibat) capsules, for oral use

NDA: 215498

In response to DG's consult request dated January 13, 2021, OPDP has reviewed the proposed product labeling (PI) for the original NDA submission for Bylvay.

Labeling: OPDP has no comments on the proposed labeling based on the draft PI received by electronic mail from DG on April 21, 2021.

Thank you for your consult. If you have any questions, please contact Meeta Patel at (301) 796-4284 or meeta.patel@fda.hhs.gov.

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic
and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatric and Maternal Health Review

Date: 4/8/2021 **Date consulted:** 12/2/2020

From: Jean Limpert, MD, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Division Director
Division of Pediatric and Maternal Health

To: Division of Hepatology and Nutrition (DHN)

Drug: Bylvay (odevixibat)

NDA: 215498

Applicant: Albireo AB/Albireo Pharma, Inc.

Subject: Pregnancy and Lactation Labeling

Proposed Indication: Treatment of pruritis in pediatric patients (age (b) (4) 3 months to 17 years) with progressive familial intrahepatic cholestasis (PFIC)

Materials Reviewed:

- DPMH consult request dated December 2, 2020, DARRTS reference ID 4710490
- Applicant's submitted background package and proposed labeling for NDA 215498

Consult Question: "Please evaluate the maternal health related sections of the labeling."

INTRODUCTION AND BACKGROUND

On November 20, 2020, Albireo AB submitted a 505(b)(1) New Drug Application (NDA) for Bylvay (odevixibat), a new molecular entity. The proposed indication is for the treatment of pruritis in pediatric patients with PFIC. On December 2, 2020, DHN consulted DPMH to assist with the Pregnancy and Lactation subsections of labeling.

Regulatory History

- Odevixibat (A4250) is a first in class ileal bile acid transporter (IBAT) inhibitor.
- Odevixibat is not currently approved in any country. IBAT inhibitors are under development for the treatment of other cholestatic liver diseases, metabolic disorders, and idiopathic chronic constipation.[1]
- Odevixibat qualified for orphan designation for treatment of PFIC, Alagille syndrome, biliary atresia, and primary biliary cholangitis (2012).
- Odevixibat qualified for pediatric disease designation and fast track designation (2018).

Drug Characteristics[2]

- Drug class: IBAT inhibitor
- Odevixibat is a small molecule that acts as reversible inhibitor of IBAT and decreases the reuptake of bile in the terminal ileum.
- The recommended dose is 40 mcg/kg administered orally once daily with meals (chronic administration). However, the drug may be titrated up to 120 mcg/kg/day for patients who do not respond to 40 mcg/kg/day.
- Odevixibat has minimal systemic absorption, but the systemic absorption may increase in a dose dependent manner. In healthy adults, plasma concentrations of odevixibat were below the limit of quantification (0.05ng/L) in the majority of samples following single and repeated oral administration up to 3mg (corresponding to approximately 43 mcg/kg). However, following a single administration of odevixibat 7.2 mg (corresponding to approximately 103 mcg/kg for a 70-kg man, 2.6 times the recommended dose) in healthy adults, peak odevixibat plasma concentration is reached between 1 to 5 hours. The Cmax and area under the concentration-time curve from 0 to 24 hours were 0.47 ng/mL and 2.19 ng*h/mL, respectively. There is no accumulation of odevixibat following once daily dosing.
- Molecular weight: 767.9 g/ml
- Half-life: 2.4 hours.
- > 99% bound to plasma proteins (in vitro).
- Most common adverse reactions: diarrhea, vomiting, and liver enzyme elevations.

Reviewer comment: DPMH discussed the clinical pharmacology findings with the Clinical Pharmacology team. Data indicate that systemic drug concentrations in healthy adults are measurable at the higher end of the proposed dose range and that systemic absorption may increase in a dose dependent manner.

[1] Karpen S. (2020). Ileal bile acid transporter inhibition as an anticholestatic therapeutic target in biliary atresia and other cholestatic disorders. *Hepatology International.*, *14*(5), 677–689.
[2] Based on applicant's proposed labeling and subsequent revisions by clinical team, 3/26/21

REVIEW

PREGNANCY

PFIC and Pregnancy

- PFIC is a group of rare autosomal recessive liver disorders associated with defects in bile secretion or transport. PFIC is estimated to affect one in 50,000 to 100,000 births.[3]
- Disease onset is typically in infancy or early childhood though patients with PFIC type 3 may have onset in young adulthood. Clinical features include cholestasis, jaundice, and pruritis. The majority of patients develop end-state liver disease and undergo liver transplantation before adulthood and typically before the age of 10. PFIC is typically fatal if untreated.[4]
- There are no approved pharmaceutical treatments for PFIC. Off-label use of medications such as ursodeoxycholic acid, cholestyramine, naltrexone, and antihistamines may be used for symptomatic relief of pruritis. The only effective treatment for patients with PFIC is surgical intervention.[5]
- The published literature reports only six cases of pregnancy in patients with PFIC, most of whom had prior surgical intervention or liver transplantation. In the reported cases, treatment of pruritis during pregnancy was managed by ursodeoxycholic acid, intermittent plasmapheresis, and/or intermittent extracorporeal albumin liver dialysis.
    - A 20-year-old pregnant person with PFIC type 2 and history of a surgical biliary diversion developed worsening cholestasis, coagulopathy, and fat-soluble vitamin deficiencies during pregnancy. She received ursodeoxycholic acid for pruritis and vitamin supplementation . She delivered at 32 2/7 weeks following preterm labor.[6]
    - A 30-year-old pregnant person with PFIC type 2 and history of ileal exclusion developed severe cholestasis and mild coagulopathy during the third trimester. She was treated with ursodeoxycholic acid and had a normal pregnancy outcome.[7]
    - A pregnant person with PFIC type 1 and history of liver transplant developed cholestasis which was successfully treated with ursodeoxycholic acid. She delivered a healthy infant.[8]
    - 23-year-old with PFIC type 3 stopped ursodeoxycholic acid when pregnant but restarted at 11 weeks' gestation due to pruritis. The pruritis was refractory to ursodeoxycholic acid as well as intermittent plasmapheresis. She ultimately required intermittent extracorporeal albumin liver dialysis for intractable

[3] Baker A, Kerkar N, Todorova L, Kamath BM, Houwen RHJ. Systematic review of progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol. 2019 Feb;43(1):20-36.

[4] Kamath, B. (2020). Potential of ileal bile acid transporter inhibition as a therapeutic target in Alagille syndrome and progressive familial intrahepatic cholestasis. *Liver International : Official Journal of the International Association for the Study of the Liver.*, *40*(8), 1812–1822.

[5] Kamath, B. (2020). Potential of ileal bile acid transporter inhibition as a therapeutic target in Alagille syndrome and progressive familial intrahepatic cholestasis. *Liver International : Official Journal of the International Association for the Study of the Liver.*, *40*(8), 1812–1822.

[6] Mahle, A. C. (2021) Severe vitamin deficiencies in pregnancy complicated by progressive familial intrahepatic cholestasis. *BMJ case reports.* [Online] 14 (3), —.

[7] Czubkowski P (2015). Successful pregnancy after ileal exclusion in progressive familial intrahepatic cholestasis type 2. Ann Hepatol. 14(4):550-2.

[8] Cash W. (2011). Successful pregnancy after liver transplantation in progressive familial intrahepatic cholestasis, type 1. *Pediatric Transplantation.*, *15*(8), E174–E176.

pruritis and delivered at 34 weeks' gestation due to preterm labor and elevated bile acids. The preterm infant was reportedly healthy.[9]

- 17-year-old pregnant person with PFIC type 1 and history of diverting ileostomy developed pruritis and cholestasis. The patient was initially treated with ursodeoxycholic acid without adequate response but was successfully treated with intermittent plasmapheresis.[10]
- 22-year-old pregnant person with PFIC type 1 developed cholestasis and pruritis during pregnancy which was successfully treated with weekly plasmapheresis. She delivered a premature infant at 33 weeks' gestation.[11]

While little is known about PFIC during pregnancy, intrahepatic cholestasis of pregnancy (ICP) is a transient form of cholestasis and includes heterozygous mutations in ATP8B1, ABCB11 and ABCB4, which are the same genes affected in PFIC. ICP is characterized by pruritis and elevation of serum bile acids, typically during the second and third trimester of pregnancy. It is hypothesized that elevated sex hormones induce cholestasis and pruritis, possibly by their inhibiting influence on major bile acid update transporters and on bile salt exposure.[12] Elevated maternal serum bile acids are associated with adverse fetal outcomes, including intrauterine demise, meconium amniotic fluid, preterm delivery, and neonatal respiratory distress syndrome. Patients are typically treated with ursodeoxycholic acid and induced at 37 weeks' gestation.[13]

Pregnancy in patients with chronic liver disorders may be challenging because of the risk of deterioration of liver function. [14] Patients with chronic liver disease are at risk for fat-soluble vitamin deficiencies, including Vitamin K deficiency which can lead to coagulopathy.[15]

Nonclinical Experience

In an embryo-fetal development study, pregnant rabbits received oral doses of 10, 30, or 100 mg/kg/day during the period of organogenesis. Fetuses from all maternal groups treated with odevixibat showed an increase in cardiovascular malformations, which included 5-chambered heart, small ventricle, large atrium, ventricular septum defect, misshapen aortic valve, dilated aortic arch, right sided and retroesophageal aortic arch, fusion of aortic arch and pulmonary

[9] Lemoine M (2008). Albumin liver dialysis as pregnancy-saving procedure in cholestatic liver disease and intractable pruritus. World J Gastroenterol.14(42):6572-4.
[10] Mathias A (2009) Progressive familial intrahepatic cholestasis complicating pregnancy, The Journal of Maternal-Fetal & Neonatal Medicine, 22:9, 816-818.
[11] Branger B (1999) Apheresis for Byler syndrome in pregnancy: tolerance and effectiveness. Ann Med Interne (Paris).150(1):70-2.
[12] cholestasis. *BMJ case reports.* [Online] 14 (3), –.
[12] van der Woerd WL (2010) Familial cholestasis: progressive familial intrahepatic cholestasis, benign recurrent intrahepatic cholestasis and intrahepatic cholestasis of pregnancy. Best Pract Res Clin Gastroenterol. 24(5):541-53.
[13] https://www.uptodate.com/contents/intrahepatic-cholestasis-of-pregnancy?search=elevated%20bile%20acids%20pregnancy&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1#H921223047
[14] Czubkowski P (2015). Successful pregnancy after ileal exclusion in progressive familial intrahepatic cholestasis type 2. Ann Hepatol. 14(4):550-2.
[15] Mahle, A. C. (2021) Severe vitamin deficiencies in pregnancy complicated by progressive familial intrahepatic cholestasis. *BMJ case reports.* [Online] 14 (3), –.

trunk, ductus arteriosus atresia, and absence of subclavian artery. These malformations occurred at low maternal systemic exposures to odevixibat (AUC [area under the concentration-time curve] of 6.28 ng•h/mL and higher). In humans, only limited systemic exposure has been detected at the recommended dose (40 mcg/kg/day). Therefore, animal and human doses should not be compared directly for evaluating relative exposure. Odevixibat was shown to cross the placenta in pregnant rats.

No adverse effects on embryo-fetal development were observed following oral administration of 100, 300, or 1000 mg/kg/day in pregnant rats during organogenesis. An increase in skeletal variations (delayed/incomplete ossification and thick ribs) was observed at 1000 mg/kg/day. Maternal systemic exposure to odevixibat at the maximum dose tested was 799 ng•h/mL in rats, whereas only limited systemic exposure has been detected in humans at the recommended dose (40 mcg/kg/day). Therefore, animal and human doses should not be compared directly for evaluating relative exposure.

No adverse effects on postnatal development were observed in a pre- and postnatal development study, in which female rats were treated orally with up to 1000 mg/kg/day during organogenesis through lactation. The maternal AUC for odevixibat at 1000 mg/kg/day was 1274 ng•h/mL

Reviewer comment: The findings were discussed with the Pharmacology/Toxicology team.[16] The assay used to measure systemic levels in rabbits was highly sensitive and the presence of cardiac malformations even at low maternal systemic exposures (AUC 6.28 ng•h/mL) is compelling. Further, the findings are also significant when comparing the incidence of cardiac malformation to a historical control group. A NOAEL could not be established.

In the pharmacokinetic studies, while the majority of patients did not have detectable systemic plasma levels at the dose of 40 mcg/kg/day, some of the participants did have measurable systemic levels. Thus, odevixibat appears to be minimally absorbed in some participants. At the human dose of 40 mcg/kg/day, a reliable human AUC could not be determined so a comparison between animal and human doses is not possible.

*At the higher dose for which there is pharmacokinetic data, the safety margin to the lowest exposure at which cardiac malformations were observed in rabbits was 2.4 fold; this is based on an AUC of 2.639 ng*hr/mL at 9.6mg (~137 mcg/kg for a 70kg adult).*

The reader is referred to the full Pharmacology/Toxicology review by Fresnida Ramos, PhD and Ke Zhang, PhD (pending).

Clinical Studies

Odevixibat has been evaluated in seven clinical studies (n=227 participants received odevixibat) including four Phase 1 studies in adults, one Phase 2 study in pediatric patients, and two Phase 3 studies in pediatric patients with PFIC. Pregnant persons were excluded from clinical trials and no pregnancies were reported in the odevixibat clinical development program.[17]

[16] Information based on discussions with Pharmacology/Toxicology team 4/7/21 and 4/8/21
[17] Applicant's Summary of Clinical Safety, page 193

Review of Literature

Applicant's Review of Literature

The applicant did not identify any publications for odevixibat and pregnancy.

DPMH Review of Literature

DPMH performed a search in PubMed, Embase, Micromedex, [18] TERIS, [19] Reprotox, [20] and Briggs[21] to find relevant articles related to the use of odevixibat during pregnancy Search terms included "odevixibat" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," "miscarriage," and "fetal loss." No relevant information was identified.

LACTATION

Nonclinical Experience

Studies in lactating rats did not assess the presence of odevixibat in milk.

The reader is referred to the full Pharmacology/Toxicology review by Fresnida Ramos, PhD and Ke Zhang, PhD (pending).

Clinical Studies

Odevixibat has been evaluated in seven clinical studies (n=227 subjects received odevixibat) including four Phase 1 studies in adults, one Phase 2 study in pediatric patients, and two Phase 3 studies in pediatric patients with PFIC. Pregnant persons were excluded from clinical trials and no cases of lactation were identified.[22]

Review of Literature

Applicant's Review of Literature

The applicant did not identify any publications for odevixibat and lactation.

DPMH review of literature

This Reviewer performed a search in PubMed, Embase, Micromedex,[23] TERIS, [24] Reprotox, [25] and Briggs, [26] *Medications and Mothers' Milk*,[27] and LactMed[28] to find relevant articles related to the use of odevixibat during lactation. Search terms included "odevixibat" AND "breastfeeding" or "lactation." No relevant information was identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

[18] https://www.micromedexsolutions.com, accessed 3/24/21
[19] Truven Health Analytics information. Teris, accessed 3/24/21
[20] Truven Health Analytics information. Reprotox, accessed 3/24/21
[21] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 3/24/21
[22] Applicant's Summary of Clinical Safety, page 193
[23] https://www.micromedexsolutions.com, accessed 3/24/21
[24] Truven Health Analytics information. Teris, accessed 3/24/21
[25] Truven Health Analytics information. Reprotox, accessed 3/24/21
[26] Briggs GG, Freeman RK. Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk. 10th edition. 2015, Philadelphia, PA. online, accessed 3/24/21
[27] https://www.halesmeds.com, accessed 3/24/21
[28] https://www.ncbi.nlm.nih.gov/books/NBK501922/, accessed 3/24/21

Nonclinical Experience
Odevixibat was not genotoxic in the Ames test and other assays. Two carcinogenicity studies did not indicate that odevixibat is a carcinogen. Fertility studies in rats did not show effects on fertility.

The reader is referred to the full Pharmacology/Toxicology review by Fresnida Ramos, PhD and Ke Zhang, PhD (pending).

Review of Pharmacovigilance Database
The applicant did not identify cases related to fertility.

Review of Literature
Applicant's Review of Literature
The applicant did not identify any publications for odevixibat and fertility.

DPMH review of literature
This Reviewer performed a search in PubMed, Embase, Reprotox to find relevant articles related to the use of odevixibat and effects on fertility. Search terms included "odevixibat" AND "fertility," "infertility," "contraception," and "oral contraceptives." No relevant information was identified.

DISCUSSION AND CONCLUSIONS
Pregnancy
There are no available data on odevixibat use in pregnant persons. In embryofetal studies, pregnant rabbits exposed to oral odevixibat during organogenesis had a corresponding increase in fetal cardiac malformations, including at low maternal systemic exposures (AUC of 6.28 ng•h/mL). A NOAEL could not be established in the rabbit embryofetal studies.

Clinical pharmacology studies indicate that at the standard treatment dose of 40 mcg/kg/day, odevixibat is minimally absorbed in some participants though the majority of participants do not have measurable systemic absorption. Due to the lack of systemic absorption in most participants, a human AUC cannot be determined at this dose and a direct comparison between human and animal doses is not possible.

Based on the cardiac malformations in rabbits even at low systemic exposures, the lack of establishment of a NOAEL, and the finding that odevixibat has minimal systemic absorption in some participants at the standard treatment dose of 40 mcg/kg, DPMH proposes to add a statement that based on animal studies, odevixibat may lead to cardiac malformations in Subsection 8.1 Risk Summary of labeling.

Pregnancy has rarely been reported in patients with PFIC since most patients will undergo liver transplantation by the age of 10 and will not require additional treatment. Given that pregnancy is unlikely in this rare disease pediatric population, a postmarketing pregnancy safety study is not recommended at this time.

Lactation

Odevixibat is minimally absorbed following oral administration, and breastfeeding is not expected to result in exposure of the infant to BYLVAY. There are no data on the presence of odevixibat in animal or human milk, the effects on the breastfed infant, or the effects on milk production. Subsection 8.2 will include standard benefit/risk statement.

Pregnancy has rarely been reported in patients with PFIC; therefore, a lactation study is not recommended at this time.

Females and Males of Reproductive Potential
Animal data in rats did not show effects on fertility. There are no human fertility data with odevixibat use in female and males of reproductive potential.

LABELING RECOMMENDATIONS
DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH discussed our labeling recommendations with the Division on April 8, 2021. DPMH recommendations are below and reflect the discussions with DHN. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION
----------USE IN SPECIFIC POPULATIONS----------
Pregnancy: Based on animal data, may cause cardiac malformations (8.1).
FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no human data on BYLVAY use in pregnant persons to establish a drug-associated risk of major birth defects, miscarriage, or adverse (b) (4) outcomes. Based on findings from animal reproduction studies, BYLVAY may cause cardiac malformations when a fetus is exposed during pregnancy. In pregnant rabbits treated with odevixibat during organogenesis, an increased incidence of malformations in fetal heart, great blood vessels, and other vascular sites occurred at all doses, (b) (4) *(see Data)*.

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. (b) (4) The background risks in the U.S. general population of major birth defects and miscarriages are 2-4% and 15-20% of clinically recognized pregnancies, respectively.

Data
Animal Data
In an embryo-fetal development study, pregnant rabbits received oral doses of 10, 30, or 100 mg/kg/day during the period of organogenesis. Fetuses from all maternal groups treated with odevixibat showed an increase in cardiovascular malformations, which included 5-chambered heart (b) (4), small ventricle, large atrium, ventricular septum defect,

misshapen aortic valve, dilated aortic arch, right sided and retroesophageal aortic arch, fusion of aortic arch and pulmonary trunk, ductus arteriosus atresia, and absence of subclavian artery. These malformations occurred at (b) (4)

Odevixibat was shown to cross the placenta in pregnant rats.

No adverse effects on embryo-fetal development were observed (b) (4) following oral administration of 100, 300, or 1000 mg/kg/day in pregnant rats during organogenesis. An increase in skeletal variations (delayed/incomplete ossification and thick ribs) was observed at 1000 mg/kg/day. Maternal systemic exposure to odevixibat at the maximum dose tested was (b) (4)

No adverse effects on postnatal development were observed in a pre- and postnatal development study, in which female rats were treated orally with up to 1000 mg/kg/day during organogenesis through lactation. The maternal AUC for odevixibat at 1000 mg/kg/day was (b) (4)

Reviewer comment: The final Pharmacology/Toxicology labeling edits are pending.

8.2 Lactation

Risk Summary

Odevixibat (b) (4) following oral administration, and breastfeeding is not expected to result in exposure of the infant to BYLVAY *[see Clinical Pharmacology (12.3)]*. There are no data on the presence of odevixibat in human (b) (4), the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for BYLVAY and any potential adverse effects on the breastfed (b) (4) from BYLVAY or from the underlying maternal condition.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JEAN L LIMPERT
04/13/2021 04:00:30 PM

MIRIAM C DINATALE
04/13/2021 04:21:49 PM

LYNNE P YAO
04/14/2021 11:15:21 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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M E M O R A N D U M

From: Shamir Tuchman, MD, MPH, Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Hepatology and Nutrition (DHN)

Subject: Review of studies submitted in support of NDA for applicability to U.S. population and input on scope of PMR safety studies

Applicant: Albireo AB[1]

Application number: NDA 215498

Drug: Odevixibat[2]

[1] This review will refer to "Albireo AB" as the "Applicant"

[2] This review will refer to the drug product as "Odevixibat"

Drug Class: Apical sodium dependent bile acid transport inhibitor (ASBTi)

Proposed Indication: Treatment of pruritus in patients with progressive familial intrahepatic cholestasis (PFIC)

Proposed Dosage Form(s): 400 mcg and 1200 mcg capsules
200 mcg and 600 mcg (b) (4)

Proposed Route of administration: Oral

Proposed Dosing Regimen: (b) (4) mcg/kg daily (maximum (b) (4))

Consult Request:
DHN requests DPMH to provide 1) an assessment of the applicability of the findings of the pivotal trial to the U.S. pediatric population with PFIC, and 2) recommendations for assessing outcomes in post-marketing safety studies designed to monitor growth and neurocognitive development in pediatric patients with PFIC taking odevixibat long-term.

Materials Reviewed:

- The following documents included for Odevixibat entered into DARRTS under NDA 215498, November 11, 2020:

    - Introduction, Module 2.2 (eCTD #1)
    - Clinical Overview, Module 2.5 (eCTD #1)
    - Summary of Clinical Efficacy, Module 2.7.3 (eCTD #1)
    - Summary of Clinical Safety Module 2.7.4 (eCTD #1)
    - Tabular Listing of all Clinical Studies, Module 5.2 (eCTD #1)
    - Study A4250-005 Synopsis, Module 5.3.5.1 (eCTD #1)
    - Study A4250-005 Clinical Study Report, Module 5.3.5.1 (eCTD #1)
    - Study A4250-005 Protocol, Module 16.1.1 (eCTD #1)
    - Study A4250-008 Synopsis, Module 5.3.5.1 (eCTD #1)
    - Study A4250-008 Clinical Study Report, Module 5.3.5.1 (eCTD #1)
    - Study A4250-008 Protocol, Module 16.1.1 (eCTD #1)
    - Orphan Drug Designation Letter, Module 1.2, (eCTD #1)
    - Rare Pediatric Disease Designation Letter, Module 1.2 (eCTD#1)

- The following documents included for Odevixibat entered into DARRTS under IND 130591

    - Fast Track Designation Letter, September 14, 2018
    - Advice/Information Request Letter dated July 20, 2020

I. Background

A. Progressive Familial Intrahepatic Cholestasis

1. Pathophysiology

PFIC is a diagnosis that is inclusive of a heterogeneous group of autosomal recessive genetic disorders associated with cholestasis due to impaired bile acid secretion and transport. PFIC presents with signs and symptoms of intrahepatic cholestasis, including jaundice and pruritis, in infancy or early childhood. PFIC is characterized by progression to end stage liver disease (ESLD) and/or the need for liver transplantation over a range of ages from infancy to adulthood.[3,4]

PFIC is generally categorized into three main subtypes, PFIC 1 to 3, based on the identified transporter mutation. PFIC 1 and PFIC 2 account for two-thirds of prevalent cases whereas PFIC 3 accounts for the remaining one-third.[5] Two further subtypes, PFIC 4 and 5, have recently been identified with research ongoing into their clinical manifestations and genotype-phenotype correlations.

PFIC 1 is caused by mutations in the ATPase phospholipid transporting 8B1 gene (ATP8B1) which encodes a phospholipid transporting transmembrane P-type adenosine triphosphatase known as FIC 1.[6] FIC 1 is located in the canalicular membrane of hepatocytes and is involved in phospholipid translocation which is important in protecting and maintaining the integrity of the membrane.[7] Genotype-phenotype correlations are incomplete in PFIC 1. Isolated case reports of mutations in ATP8B1 leading to less severe impairment in the protein function have been documented in

[3] Srivastava A. Progressive familial intrahepatic cholestasis. J Clin Exp Hepatol. 2014;4(1):25-36.

[4] Baker A, Kerkar N, Todorova L, et al. Systematic review of progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol. 2019 Feb;43(1):20-36.

[5] Davit-Spraul A, Gonzales E, Baussan C, Jacquemin E. Progressive familial intrahepatic cholestasis. Orphanet J Rare Dis. 2009 Jan 8;4:1

[6] Bull LN, van Eijk MJ, Pawlikowska L, et al. A gene encoding a P-type ATPase mutated in two forms of hereditary cholestasis. Nat Genet. 1998 Mar;18(3):219-24.

[7] Paulusma ML, Groen A, Kunne C, et al. Atp8b1 deficiency in mice induces resistance of the canalicular membrane to hydrophobic bile salts and impairs bile acid transport. Hepatology. 2006;44:195-204.

patients with milder phenotypes, but, for the majority of described mutations, there is not a well-characterized genotype-phenotype correlation that enables prediction of symptom severity and response to treatment.[8, 9]

PFIC 2 is caused by mutations in the ATP binding cassette sub-family B member11 gene (ABCB11) which encodes the bile salt export pump (BSEP), the main transporter of bile acids from hepatocytes to the canalicular lumen.[10] Defects in BSEP synthesis and/or function lead to reduced bile salt secretion followed by decreased bile flow, accumulation of bile salts in hepatocytes and hepatocellular damage.[11] Distinct clinical phenotypes (e.g. BSEP 1, BSEP 2, and BSEP 3) having been described in the literature for the location and type of certain mutations that have implications for the clinical presentation and potential response to therapy. Missense mutations in ABCB11 in less conserved regions lead to a milder phenotype.[12]

Assessment of genotype-phenotype correlations have been published for the largest genetically defined cohort of PFIC 2 patients with ABCB11 mutations leading to differences in BSEP functionality.[13] Patients with at least one of two mutations, commonly found in European PFIC cohorts (D482FG and E297G) associated with residual BSEP function (BSEP 1), are less likely to present with jaundice or develop portal hypertension, and survive to an older age before receiving a liver transplant.[14,15] They were also more likely to achieve partial or complete sustained relief of pruritis after biliary diversion.[16] Patients with mutations leading to non-functional BSEP (BSEP 3) had

[8] Klomp LW, Vargas JC, van Mil SW, et al. Characterization of mutations in ATP8B1 associated with hereditary cholestasis. Hepatology. 2004;40:27–38.

[9] Houwen RH, Baharloo S, Blankenship K, Raeymaekers P, Juyn J, Sandkuijl LA, Freimer NB. Genome screening by searching for shared segments: mapping a gene for benign recurrent intrahepatic cholestasis. Nat Genet. 1994 Dec;8(4):380-6

[10] Strautnieks SS, Bull LN, Knisely AS, et al. A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis. Nat Genet. 1998 Nov;20(3):233-8.

[11] See footnote 3

[12] Lam P, Soroka CJ, Boyer JL. The bile salt export pump: clinical and experimental aspects of genetic and acquired cholestatic disease. Semin Liver Dis. 2010;30:125–133.

[13] van Wessel DBE, Thompson RJ, Gonzales E et al.; NAtural course and Prognosis of PFIC and Effect of biliary Diversion (NAPPED) consortium. Genotype correlates with the natural history of severe bile salt export pump deficiency. J Hepatol. 2020 Jul;73(1):84-93

[14] Hayashi H, Takada T, Suzuki H, Akita H, Sugiyama Y. Two common PFIC2 mutations are associated with the impaired membrane trafficking of BSEP/ABCB11. Hepatology. 2005 Apr;41(4):916-24. 8

[15] Pawlikowska L, Strautnieks S, Jankowska I, et al. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. J Hepatol. 2010 Jul;53(1):170-8

[16] Ibid

no relief of pruritis after biliary diversion potentially limiting its usefulness for pruritis in this sub-group of PFIC patients.[17]

PFIC 3 is a bile acid secretion disorder that differs from PFIC 1 and 2 in clinical presentation and laboratory findings (e.g. high gamma glutamyl transpeptidase (GGT)). It is caused by mutations in the adenosine triphosphate-binding cassette, subfamily B, member 4 (ABCB4) gene encoding a multidrug resistance class III (MDR3) protein.[18] MDR3 is a phospholipid translocating protein. The protein facilitates biliary secretion of phospholipids which are responsible for neutralizing the detergent effects of bile salts. Mutations in MDR3 lead to defective neutralization of bile salts causing injury to the biliary epithelium and bile canaliculi which results in cholestasis.[19] As in PFIC 1 and 2, depending on the nature of the mutations in ABCB4, milder disease phenotypes do occur.

In general, patients with PFIC 1 and 2 present with more severe signs and symptoms of cholestasis occurring earlier in life. The clinical presentation, course and laboratory measures overlap between PFIC 1 and 2. PFIC 1 and 2 share common abnormal laboratory findings including low-to-normal GGT, normal serum cholesterol, elevated serum primary bile acids, and low biliary primary bile acid concentrations such as chenodeoxycholic acid.[20] Important distinguishing features of PFIC 1 compared with PFIC 2 are the presence of extra-hepatic manifestations such as diarrhea, pancreatitis, pneumonia, and hearing loss in PFIC 1 and the occurrence of cholelithiasis and hepatocellular carcinoma in PFIC 2.[21] Pruritis, which is one of the most debilitating symptoms of disease, results in excoriation and hyperpigmentation of the skin, irritability, poor sleep, and impaired attention resulting in poor academic performance.[22] Pruritis occurs in both PFIC 1 and 2 without clear-cut differences in the evolution of this symptom between the two diseases.[23] In addition to signs and symptoms of cholestasis,

[17] Ibid

[18] Davit-Spraul A, Gonzales E, Baussan C, Jacquemin E. The spectrum of liver diseases related to ABCB4 gene mutations: pathophysiology and clinical aspects. Semin Liver Dis. 2010 May;30(2):134-46

[19] de Vree JM, Jacquemin E, Sturm E, Cresteil D, Bosma PJ, Aten J, Deleuze JF, Desrochers M, Burdelski M, Bernard O, Oude Elferink RP, Hadchouel M. Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis. Proc Natl Acad Sci U S A. 1998 Jan 6;95(1):282-7

[20] Jacquemin E. Progressive familial intrahepatic cholestasis. Clin Res Hepatol Gastroenterol. 2012 Sep;36 Suppl 1:S26-35.

[21] See footnote 15

[22] See footnote 3

[23] Davit-Spraul A, Fabre M, Branchereau S, Baussan C, Gonzales E, Stieger B, Bernard O, Jacquemin E. ATP8B1 and ABCB11 analysis in 62 children with normal gamma-glutamyl transferase progressive familial intrahepatic cholestasis (PFIC): phenotypic differences between PFIC1 and PFIC2 and natural history. Hepatology. 2010 May;51(5):1645-55

patients with PFIC 1 and 2 may manifest consequences of fat malabsorption including poor growth and fat-soluble vitamin (FSV) deficiency.

2. Epidemiology

PFIC is responsible for 10-15% of cases of pathologic neonatal cholestasis syndromes. The prevalence of PFIC is estimated to be approximately one in every 50,000 to 100,000 children born worldwide and 1 per 143,000 in Europe.[24,25] PFIC 1 and 2 represent approximately two thirds of PFIC cases.[26] There have been no studies directly comparing the prevalence of genetically-confirmed PFIC between the U.S., European, and worldwide populations. Independent studies of infants and children with cholestasis have estimated the proportion of patients with PFIC at 11.7%. 12.9%, and 9% in the U.S., Swedish, and worldwide populations respectively.[27,28,29] Studies in the U.S. and Europe have generally documented PFIC 2 to be more common than PFIC 1 but a study conducted in Japan noted that PFIC 1 was the most common subtype in that population.[30] As an autosomal recessive disease, PFIC occurs more commonly in less genetically diverse populations.[31,32] A definitive pattern of clustering of ATP8B1 mutations among different ethnic populations of PFIC 1 patients has not been identified other than instances of familial clustering from a founder effect.[33]

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[24] Davit-Spraul A, Gonzales E, Baussan C, Jacquemin E. Progressive familial intrahepatic cholestasis. Orphanet J Rare Dis. 2009 Jan 8;4:1

[25] See foootnote 4

[26] Baussan C, Cresteil D, Gonzales E, et al. Genetic cholestatic liver diseases: the example of progressive familial intrahepatic cholestasis and related disorders. Acta Gastroenterol Belg. 2004 Apr-Jun;67(2):179-83

[27] Kamath BM, Chen Z, Romero R, et al. Childhood Liver Disease Research Network (ChiLDReN). Quality of Life and Its Determinants in a Multicenter Cohort of Children with Alagille Syndrome. J Pediatr. 2015 Aug;167(2):390-6.e3

[28] Fischler B, Papadogiannakis N, Nemeth A. Aetiological factors in neonatal cholestasis. Acta Paediatr. 2001 Jan;90(1):88-92.

[29] Ruth ND, et al. Identifying incidence of inherited metabolic disorders in patients with infantile liver disease. J Hepatol 2014;1:S505.

[30] Hori T, Egawa H, Takada Y, et al. Progressive familial intrahepatic cholestasis: a single-center experience of living-donor liver transplantation during two decades in Japan. Clin Transplant. 2011 Sep-Oct;25(5):776-85.

[31] Nielsen IM, Eiberg H. Cholestasis Familiaris Groenlandica: an epidemiological, clinical and genetic study. Int J Circumpolar Health. 2004;63 Suppl 2:192-4

[32] Shagrani M, Burkholder J, Broering D, et al. Genetic profiling of children with advanced cholestatic liver disease. Clin Genet. 2017 Jul;92(1):52-61

[33] See footnote 8

3. Fat-soluble Vitamin Deficiency in PFIC

FSV deficiency is part of the clinical presentation in all forms of PFIC. These may lead to complications such as bleeding from vitamin K deficiency and rickets from vitamin D deficiency. The prevalence of FSV deficiency among patients with PFIC is not well characterized. However, in a larger population of pediatric patients with chronic cholestasis, which included 39% PFIC diagnoses, the prevalence of vitamins A, D, E, and K deficiency on conventional FSV supplementation was 74%, 92%, 91%, and 20%, respectively.[34] In general, FSV deficiency manifest at an earlier age in PFIC 2.[35] FSV deficiency may also be present in the absence of other signs of cholestasis such as jaundice.[36] The etiology of certain FSV deficiencies such as vitamin D deficiency may be multifactorial. In addition to dietary vitamin D malabsorption, reduced synthesis of vitamin D binding protein, decreased sun exposure, and decreased hydroxylation of vitamin D with hepatic fibrosis play a role in the development of vitamin D deficiency.[37]

4. Growth in PFIC

Growth is significantly impaired in patients with PFIC due to a combination of malabsorption, cholestasis, and progressive liver failure. Over 95% of patients with PFIC have short stature even though their weight for height may be normal.[38] Growth failure may develop over time as approximately 50% of patients examined prior to 6 months of age had height for age at the 10th percentile or lower.[39] Due, in part, to extraintestinal manifestations associated with the disease, patients with PFIC 1 may have growth impairment beyond that attributable to cholestasis.[40] Assessment of weight as an index of growth is problematic in patients with chronic liver disease due to either the presence of ascites/edema or organomegaly confounding this measure.[41] Studies evaluating

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[34] Shen YM, Wu JF, Hsu HY, et al. Oral absorbable fat-soluble vitamin formulation in pediatric patients with cholestasis. J Pediatr Gastroenterol Nutr. 2012 Nov;55(5):587-91.

[35] See footnote 15

[36] See footnote 24

[37] Feranchak AP, Ramirez RO, Sokol RJ. Medical and nutritional management of cholestasis. In Suchy FJ, Sokol RJ, Balistreri WF, eds. *Liver disease in children*, 2nd ed. Baltimore: Lippincott Williams & Wilkins, 2001:215–7

[38] Whitington PF, Freese DK, Alonso EM, Schwarzenberg SJ, Sharp HL. Clinical and biochemical findings in progressive familial intrahepatic cholestasis. J Pediatr Gastroenterol Nutr. 1994 Feb;18(2):134-41.

[39] Naveh Y, Bassan L, Rosenthal E, et al. Progressive familial intrahepatic cholestasis among the Arab population in Israel. J Pediatr Gastroenterol Nutr. 1997 May;24(5):548-54.

[40] Bull LN, Thompson RJ. Progressive Familial Intrahepatic Cholestasis. Clin Liver Dis. 2018 Nov;22(4):657-669.

[41] Sokol RJ, Stall C. Anthropometric evaluation of children with chronic liver disease. Am J Clin Nutr. 1990 Aug;52(2):203-8.

interventions, such as biliary diversion and liver transplantation, to improve the clinical status in PFIC patients have used the absolute change in height and height z-scores as measures of improvement in growth.[42,43]

5. Neurocognitive Outcomes in PFIC

The etiology of impaired neurocognition in pediatric patients with cholestatic liver disease, including those with PFIC, is not known, and studies assessing the neurocognitive outcomes in these patients are sparse. The majority of neurocognitive studies in pediatric chronic liver disease patients have focused on outcomes after liver transplantation.[44,45] A pilot study assessing school readiness in children 3 to 6 years of age with and without liver transplants with chronic cholestatic liver disease, including PFIC, used a combination of both patient and parental assessments to assess school readiness.[46] Children were administered the Weschler Preschool and Primary Scale of Intelligence, the NEPSY-II Developmental Neuropsychological Assessment, and the Beery-Buktenica Visual-Motor Integration tests. Parents completed the Vineland-11, BASC-II, and BRIEF surveys of adaptive behavior and executive functioning. The study found that chronic cholestatic liver disease impacted acquisition of early motor, cognitive, and academic proficiency.[47]

6. Treatment

Medical therapy for PFIC involves providing for relief of symptoms of cholestasis such as pruritis, optimizing nutritional status, supplementing vitamins, and treating complications of progressive liver disease. Total caloric intake is targeted at 125% of the recommended daily allowance (RDA). Dietary fat is provided as medium chain

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[42] Melter M, Rodeck B, Kardorff R, et al. Progressive familial intrahepatic cholestasis: partial biliary diversion normalizes serum lipids and improves growth in noncirrhotic patients. Am J Gastroenterol. 2000 Dec;95(12):3522-8.

[43] D'Antiga L, Moniz C, Buxton-Thomas M, Cheeseman P, et al. Bone mineral density and height gain in children with chronic cholestatic liver disease undergoing transplantation. Transplantation. 2002 Jun 15;73(11):1788-93.

[44] Ee LC, Lloyd O, Beale K, Fawcett J, Cleghorn GJ. Academic potential and cognitive functioning of long-term survivors after childhood liver transplantation. Pediatr Transplant. 2014 May;18(3):272-9.

[45] Kaller T, Langguth N, Petermann F, Ganschow R, Nashan B, Schulz KH. Cognitive performance in pediatric liver transplant recipients. Am J Transplant. 2013 Nov;13(11):2956-65.

[46] Gold A, Rogers A, Cruchley E, Rankin S, Parmar A, Kamath BM, Avitzur Y, Ng VL. Assessment of School Readiness in Chronic Cholestatic Liver Disease: A Pilot Study Examining Children with and without Liver Transplantation. Can J Gastroenterol Hepatol. 2017;2017:9873945.

[47] Ibid

triglycerides. Water soluble vitamins are supplemented at 1 to 2 times the RDA and vitamins A, D, E, and K are supplemented at differing levels with adjustments made based on monitoring of serum levels.[48]

Pharmacologic options for the treatment of pruritis are currently limited to ursodeoxycholic acid (UDCA), rifampicin, and cholestyramine. UDCA, a hydrophilic bile acid which is not toxic to hepatocytes, is supplemented to replace hydrophobic bile acids. This is thought to cause less damage to bile canaliculi. Chronic supplementation can raise the proportion of hydrophobic bile acids in serum to upwards of 40%.[49] Approximately 58% of patients with PFIC treated with UDCA had an improvement or resolution of pruritis.[50] An improved response to UDCA in PFIC 1 and 2 has been associated with the presence of a missense mutation in at least one allele.[51] Rifampicin induces CYP3A4 expression leading to increases in 6α-hydroxylation of bile salts which are then glucuronidated and excreted in the urine. In addition, rifampicin increases the conjugation and excretion of bilirubin. Despite these effects, rifampicin has not been shown to provide sustained reductions in bilirubin and transaminases but has been shown to improve pruritis in a proportion of patients with cholestasis.[52] Hepatotoxicity represents an important limiting toxicity of rifampicin administration. Cholestyramine is a bile salt binding exchange resin that reduces absorption of bile salts thereby preventing a portion of their enterohepatic circulation. It has not been shown to be useful in improving signs and symptoms of cholestasis in PFIC.[53] UDCA, rifampicin, and cholestyramine are not currently approved for treatment of PFIC.[54]

Surgical management of PFIC includes interventions that decrease enterohepatic circulation through biliary diversion. However, improvement in pruritis with biliary diversion is not consistent across PFIC types and across BSEP subtypes within the PFIC

[48] Feranchak AP, Ramirez RO, Sokal RJ. Medical and Nutritional Management of Cholestasis. In: Suchy FJ, Sokol RJ, Balistreri WF, eds. Liver Disease in Children. 2nd ed. Lippincott, Williams and Wilkins; 2001:195–238 [Chapter 10].

[49] Jacquemin E, Hermans D, Myara A, Habes D, Debray D, Hadchouel M, Sokal EM, Bernard O. Ursodeoxycholic acid therapy in pediatric patients with progressive familial intrahepatic cholestasis. Hepatology. 1997 Mar;25(3):519-23.

[50] Ibid

[51] See footnote 15

[52] Yerushalmi B, Sokol RJ, Narkewicz MR, Smith D, Karrer FM. Use of rifampin for severe pruritus in children with chronic cholestasis. J Pediatr Gastroenterol Nutr. 1999 Oct;29(4):442-7

[53] Stapelbroek JM, van Erpecum KJ, Klomp LW, Houwen RH. Liver disease associated with canalicular transport defects: current and future therapies. J Hepatol. 2010 Feb;52(2):258-71

[54] Found under Ursodiol, Rifampin, and Cholestyramine at Drugs@FDA.gov

2 patient population,[55,56] underscoring the continued unmet medical need for additional therapies for treatment of pruritus in PFIC. The serum bile acid concentration can reduce with successful biliary diversion surgery.[57] Partial external biliary diversion (PEBD), if done prior to the development of cirrhosis, has resulted in improved growth, improvement in liver function, improvement of serum bile acids, and slowed progression of fibrosis on liver histology in patients with PFIC 1 and 2.[58] In addition to the surgical complications, fluid and electrolyte abnormalities can occur after PEBD.

Liver transplantation represents the final therapeutic option for patients with PFIC that progress to ESLD or have poor quality of life due to pruritis refractory to medical and surgical treatment. Liver transplant improves symptoms of cholestasis in over 75% of patients, irrespective of PFIC subtype.[59,60] However, due to the potential exacerbation of extra-intestinal manifestations of disease, liver transplantation may not uniformly benefit patients with PFIC 1 who can develop worsening diarrhea, graft steatosis, and a lack of catch-up growth.[61,62] Liver transplantation in PFIC 2 is more consistently beneficial.[63]

II. NDA 215498

A. Drug Product:

The ileal bile acid transporter (IBAT), alternatively known as the apical sodium-dependent bile acid transporter (ASBT), is a luminal epithelium glycoprotein expressed mainly in the distal ileum that co-transports sodium and bile acids, moving bile acids from the lumen of the small intestine across the apical brush border membrane with

[55] See footnote 15

[56] See footnote 3

[57] Schukfeh N, Metzelder ML, Petersen C, Reismann M, Pfister ED, Ure BM, Kuebler JF. Normalization of serum bile acids after partial external biliary diversion indicates an excellent long-term outcome in children with progressive familial intrahepatic cholestasis. J Pediatr Surg. 2012 Mar;47(3):501-5

[58] Davis AR, Rosenthal P, Newman TB. Nontransplant surgical interventions in progressive familial intrahepatic cholestasis. J Pediatr Surg. 2009 Apr;44(4):821-7

[59] Aydogdu S, Cakir M, Arikan C, et al. Liver transplantation for progressive familial intrahepatic cholestasis: clinical and histopathological findings, outcome and impact on growth. Pediatr Transplant. 2007 Sep;11(6):634-40

[60] Englert C, Grabhorn E, Richter A, Rogiers X, Burdelski M, Ganschow R. Liver transplantation in children with progressive familial intrahepatic cholestasis. Transplantation. 2007 Nov 27;84(10):1361-3

[61] Miyagawa-Hayashino A, Egawa H, Yorifuji T, et al. Allograft steatohepatitis in progressive familial intrahepatic cholestasis type 1 after living donor liver transplantation. Liver Transpl. 2009 Jun;15(6):610-8

[62] Lykavieris P, van Mil S, Cresteil D, Fabre M, et al. Progressive familial intrahepatic cholestasis type 1 and extrahepatic features: no catch-up of stature growth, exacerbation of diarrhea, and appearance of liver steatosis after liver transplantation. J Hepatol. 2003 Sep;39(3):447-52.

[63] See footnote 15

subsequent shuttling to the basolateral membrane, ultimately returning to the liver via portal venous blood. IBAT is responsible for 95% of the bile acids that are returned to the liver via enterohepatic circulation on a daily basis and therefore is a key regulator of the bile acid pool.[64,65]

The Applicant states that odevixibat is a small molecule that selectively inhibits IBAT without affecting other bile acid transporters. The Applicant purports that odevixibat is orally administered and acts locally in the gut where it binds reversibly to IBAT to decrease the reuptake of bile acids, increasing the clearance of bile acids through the colon, and thereby lowering the hepatic bile acid load. The Applicant further contends that the decrease in bile acid recirculated to the liver reduces bile acid levels with an associated improvement in cholestasis and reduction in pruritis.

The Division notes that odevixibat, as an inhibitor of IBAT, can substantially reduce the bile acid pool by promoting bile acid excretion thru the stool without the ability of the liver to overcome the excessive loss with de-novo production.[66,67] With a further reduction in the circulating bile acid pool with odevixibat, the Division states that patients with PFIC are potentially at risk for worsening of underlying fat and FSV malabsorption leading to potential adverse effects on growth and neurocognitive outcomes.

B. Clinical Studies Supporting Odevixibat Efficacy and Safety in Pediatric PFIC Patients:

NDA 215498 contains pivotal data from three pediatric trials to support approval of odevixibat for the proposed indication. These trials consist of a phase 2 trial in pediatric patients with cholestatic liver disease (Study A4250-003), a 24-week phase 3 trial (Study A4250-005), and a 72-week open-label long-term safety trial in pediatric patients with PFIC (Study A4250-008).

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[64] Dawson PA, Haywood J, Craddock AL, et al. Targeted deletion of the ileal bile acid transporter eliminates enterohepatic cycling of bile acids in mice. The Journal of biological chemistry. 2003;278(36):33920-33927.

[65] Hofmann AF. The enterohepatic circulation of bile acids in mammals: form and functions. Front Biosci (Landmark Ed). 2009;14:2584-2598.

[66] Graffner H, Gillberg PG, Rikner L, Marschall HU. The ileal bile acid transporter inhibitor A4250 decreases serum bile acids by interrupting the enterohepatic circulation. Aliment Pharmacol Ther. 2016 Jan;43(2):303-10.

[67] See footnote 64.

1. Study A4250-003

Study A4250-003 was a phase 2 trial of odevixibat use in pediatric patients with cholestatic liver disease. The trial evaluated 5 dose levels of odevixibat ranging from 10 to 200 mcg/kg/day administered orally once daily for 4 weeks in 20 patients with cholestatic pruritis. Ten of the 20 patients had a diagnosis of PFIC. The trial collected both pharmacodynamic (PD) and safety endpoints. PD endpoints collected included serum bile acids, pruritis and sleep-related endpoints. Study A4250-003 helped inform dose selection for the pivotal phase 3 trial of odevixibat. The doses of 40 and 120 mcg/kg/day were selected based on demonstration of a reduction in bile acids and improvement in pruritis at doses matching three-times the 50% IBAT inhibitory dose (i.e. 40 mcg/kg/day) and the 90% IBAT inhibitory dose (i.e. 120 mcg/kg/day) confirmed from the phase 1 dose-finding, PK, and PD study conducted in healthy adults (Study A4250-001).

2. Study A4250-005

The primary data in support of efficacy of odevixibat comes from Study A4250-005. This was a multicenter, multinational, randomized, double-blind, placebo-controlled trial which enrolled 62 pediatric patients with a clinical diagnosis of PFIC 1 or PFIC 2. The trial evaluated 2 dose levels of odevixibat (40 and 120 mcg/kg/day) and placebo administered for 24 weeks. The trial included a 35- to 56-day screening period followed by a 24-week treatment period and a 4-week follow-up period. Patients were eligible to participate if they were between 6 months and 18 years of age, had a confirmed genetic diagnosis of PFIC 1 or 2 through identification of biallelic pathogenic variants in either the ATP8B1 or ABCB11 genes. Patients in Study A4250-005 were required to have serum bile acids greater the 100 µmol/L at baseline and a history of significant pruritus as defined by a caregiver-reported observed scratching score of greater than or equal to 2 in the 2 weeks prior to randomization. Patients with pathologic variations of the ABCB11 gene that predict complete absence of the BSEP protein (i.e. BSEP 3) and a history of either biliary diversion (within 6 months of screening) or a liver transplant were excluded from participation. Patients were randomized 1:1:1 to placebo, 40 or 120 mcg/kg/day of odevixibat. Patients were stratified by age (6 months to 5 years, 6 to 12 years, and 13 to less than or equal to 18 years of age) and PFIC type (1 and 2). Stable dosing of concomitant therapies such as UDCA and rifampicin were allowed in the trial. The initial trial design allowed patients without improvement or with intolerable symptoms to roll-over into Study A4250-008 after 12 weeks and receive the 120 mcg/kg/day dose. This provision was subsequently removed from the protocol to protect the validity of the final study results when the Applicant noted that a subset of patients who had rolled over early into Study A4250-008 had not experienced worsening of symptoms as required in the

protocol. Study patients who rolled over prior to the protocol revision were classified as non-responders for serum bile acid and pruritis assessments.

The primary efficacy assessment in Study A4250-005 was the proportion of positive pruritis assessments over the 24-week treatment period. A positive pruritis assessment is defined as a scratching score less than or equal to 1 or at least a 1-point drop in the score on the Observer Reported Outcome (ObsRO) instrument. The Applicant developed the clinical outcome assessment tool, including Patient Reported Outcomes (PRO) and ObsRO instruments, to assess pruritus (itching and scratching, respectively). These instruments also evaluated sleep disturbance. Itching, scratching, and sleep disturbance were recorded twice daily (AM and PM) by a caregiver for all patients using the ObsRO instrument and in addition using the PRO instrument for patients older than 7 years of age. Secondary efficacy endpoints analyzed from the trial include changes in hepatic biochemical parameters, sleep parameters, growth velocity as defined by changes in height z-score, and the proportion of patients undergoing biliary diversion and/or liver transplantation. Included in the safety assessment were measures of vitamin A, D, E, and K (e.g. INR) at screening/baseline, week 12 and week 24.

3. Study A4250-008

Additional data in support of odevixibat safety comes from Study A4250-008. This is an ongoing, long-term, 72-week, open-label extension trial for patients rolled over from Study A4250-005 and for additional patients with PFIC (any type) who were not eligible for or were identified after enrollment closed for Study A4250-005. Study A4250-008 is evaluating treatment with odevixibat administered at the 120 mcg/kg/day dose. The Applicant pooled data from all patients in Study A4250-005 and those patients who have completed the 72-week follow-up (some of whom rolled over from Study A4250-005) in Study A4250-008 for safety analyses. The pooled safety analysis was based on 69 patients with PFIC who were dosed in Study A4250-008, consisting of 53 who had received treatment in Study A4250-005 and 16 newly enrolled patients.

4. Odevixibat Regulatory History:

FDA granted odevixibat Orphan Drug Designation on October 31, 2012 for the treatment of PFIC and Rare Pediatric Disease Designation on June 4, 2018. FDA granted Fast Track Designation for treatment of pruritis associated with PFIC on September 14, 2018. On October 19, 2020, the FDA held a Type B meeting teleconference with the Applicant. As part of the responses to the Applicant's questions, the FDA noted that "only 8 out of 62 patients in the pediatric trials were enrolled from the U.S. with the remaining subjects

enrolled in Europe or the rest of the world. The FDA requested the Applicant to provide a rationale for the applicability of the trial population studied to the US population." In addition, the FDA stated that because the primary objective and pre-specified efficacy endpoint in the pivotal Study A4250-005 was to evaluate the effect of odevixibat on pruritis, the data to support a broader indication of "treatment of PFIC" (b) (4) were not supported. Furthermore, the FDA clarified that (b) (4) In addition, the FDA recommended in an Advice Letter that the Applicant perform neurological assessments in Study A4250-008 that would be acceptable for all ages of the enrolled population and that these tests should be performed by providers with expertise in neurocognitive assessments.

The FDA also disagreed with (b) (4) The FDA noted that it was not possible to differentiate drug-induced FSV deficiency versus disease-mediated FSV deficiency. The FDA advised the Applicant to compare FSV deficiency in the respective treatment arms to the placebo treatment arm and that such comparisons, along with a prior medical history of FSV deficiency, should include an estimation of FSV deficiency severity along with details of how study patients were supplemented with FSV.

5. U.S. Study Population in the Overall Study Population in Odevixibat Phase 3 Trials

Overall, 11 (14%) of the 78 patients enrolled in Studies A4250-005 and A4250-008 were from the U.S. For the pivotal trial, Study A4250-005, 8 (13%) of the 62 patients were enrolled at U.S. sites. All patients in the Phase 3 studies who were included in the primary efficacy and safety assessments were genetically confirmed to have PFIC 1, 2, or 3 with the mutations leading to specific deficits in the FIC1, BSEP, and MDR3 protein, respectively. The Applicant stipulates that the specific genetic mutations in patients with PFIC led to the phenotypic presentation and as a result, differences by region in disease presentation or in response to treatment with odevixibat are not expected.

6. PFIC Subtypes in Study A4250-005

Eighteen unique mutations were found on the ATP8B1gene in the 17 PFIC 1 study patients. Among the PFIC 1 patients, the p.Ala1208ProFsTer (17.7%), a deletion mutations, and p.Gly308Val (17.7%) mutation were the most common. Among the PFIC 2 patients, p.E297G (11.1%) and p.D482G (7.8%) were the most common mutations.

Fifty percent of U.S. patients had PFIC 2 in Study A4250-005 as compared with 71% from Europe, and 84% for the rest of the world. As shown in **Table 1**, of the PFIC 2 patients enrolled, the proportions of BSEP 1 among the 3 regions was similar understanding direct statistical comparison were not possible given the smaller number of patients enrolled from the U.S.

Table 1: Regional Distribution of BSEP Subtypes of PFIC 2 Patients in Study A4250-006

BSEP Subtype	Region			
	U.S.	European Union	Rest of the World	Total
BSEP 1	1 (25%)	8 (32%)	3 (19%)	12
BSEP 2	3 (75%)	17 (68%)	13 (81%)	33
	4 (100%)	25 (100%)	16 (100%)	45

III. Discussion:

- **Applicability of the data submitted in NDA 215498 to the U.S. Pediatric Population with PFIC:**

The applicability of the data submitted in NDA 215498, which was generated primarily at sites outside the U.S., to the U.S. pediatric population with PFIC is dependent on potential differences in the severity of pruritis (primary endpoint) and more importantly its responsiveness to odevixibat between the U.S. and non-U.S. PFIC populations. Studies A4250-005 and A4250-008 enrolled PFIC 1 and 2 patients with Study A4250-008 also allowing enrollment of other PFIC subtypes. Published literature does not support a definitive genotype-phenotype correlation in PFIC 1. For PFIC 2, patients with mutations in D482FG and E297G, which are overrepresented in the European PFIC population, may present with a milder phenotype (BSEP1) (e.g. less severe pruritis) and potentially better responsiveness to current therapies such as UDCA and biliary diversion. Because inclusion criteria in Study A4250-005 required a history of at least moderate pruritus as defined by a caregiver-reported observed scratching score of greater than equal to 2 in the 2 weeks prior to randomization, PFIC patients with missense mutations leading to a phenotype with mild pruritis were likely excluded from participation. Also, the proportion of enrolled patients who had moderate pruritis (e.g. pruritis score less than 3) and severe pruritis (e.g. pruritis score greater than or equal to 3) in Study A4250-005 were evenly distributed (54% versus 46%, respectively) across the entire study cohort.

Whether patients with missense mutations leading to partial protein function in PFIC have improved responsiveness for pruritis with odevixibat treatment is unknown. The

relatively small size of the patient cohorts in Studies A4250-005 makes statistical comparisons of odevixibat effectiveness between patients within PFIC 1 and PFIC 2 cohorts difficult.

- **Assessing growth in a safety PMR:**

Growth in a healthy pediatric population is generally defined by increases in length/height and weight. PFIC, as a potentially progressive liver disease, may be associated with weight gain in children due to fluid retention, from ascites/peripheral edema and/or from the presence of organomegaly. Therefore, an accurate assessment of growth in these patients may be limited to changes in height. As a serious chronic medical condition, PFIC would be expected to cause slowed gain in length/height (e.g. linear growth) in a large proportion of affected pediatric patients. The degree to which linear growth is affected could potentially vary by PFIC type, the presence of residual protein functionality for a given patient's gene mutation, the presence of extra-hepatic manifestations of disease, and the effectiveness of standard-of-care therapies and nutritional supplementation provided. There are no currently validated growth charts for specific use in pediatric patients with PFIC. Assessment of linear growth, as a result, is done through comparison to a general pediatric population based on calculation of a height standard deviation score (height z-score). The effect on growth of the disease and it's treatment cannot be separated easily in PFIC. Therefore, a PMR assessing effects on growth with odevixibat as a single-arm trial should use a patient's individual growth trajectory prior to and after initiation of odevixibat.

Growth is not a rapid process and requires an assessment timeline measured in months to years to understand if the process is proceeding normally or in an abnormal fashion. The timelines for assessment may be necessarily compressed in the youngest patients where normative data are available for changes occurring in weeks to months.

The Applicant measured both height/length and weight in the pivotal phase 3 trial of odevixibat use in pediatric patients (Study A4250-005). However, the treatment period of 24 weeks was insufficient to assess the effect on growth of odevixibat relative to the placebo comparator group. The 72-week open-label long-term extension trial (Study A4250-008) collected height/length and weight as well as repeated measures of vitamin A, 25-hydroxy vitamin D, E, and K (e.g. INR) levels. Assessment of growth and the potential effects of FSV deficiencies on this outcome may inform the need for and potential design of a subsequent PMR to assess growth in the PFIC population with odevixibat use.

- **Assessing neurocognitive outcomes in a safety PMR:**

There are no published, validated measurement tools to assess neurocognitive outcomes specifically in pediatric patients with cholestatic liver disease. Assessment of neurocognitive outcomes, where published in this population before or after liver transplantation, have used standardized measurement tools developed in otherwise healthy children or those with neurocognitive deficits irrespective of underlying cause.

Neurocognitive deficits may occur throughout the pediatric age range, and whether or not odevixibat's potential effects on neurocognition would develop in a particular sensitive age window in patients with cholestatic liver disease is unclear. This is an important consideration given that assessment tools are validated for specific age ranges. As a general principle, drugs and/or toxins that affect cognition have greater effect with earlier ages of exposure in childhood. Furthermore, the duration over which neurocognitive assessments are undertaken must take into account the length of time required to detect meaningful change. This may be influenced both by the age of the patients to be studied and the sensitivity of the measurement tool to detect differences over a given time period.

The Applicant did not assess neurocognitive outcomes in the pivotal phase 3 trial (Study A4250-005) or long-term extension (Study A4250-008) of odevixibat. As such, evidence of worsening FSV deficiency and/or fat malabsorption with odevixibat cannot be tied to neurocognitive outcomes from the present submission. As a result, a safety PMR evaluating the effect of odevixibat on neurocognition may be needed.

Patients with PFIC who may derive clinical benefit from odevixibat use have likely not been assessed for neurocognitive development at pre-specified ages using consistent measurement tools. Therefore, obtaining prior neurocognitive assessments in each patient outside the confines of a safety PMR may be difficult. With this understanding, a safety PMR assessing neurocognitive outcomes should include a baseline assessment using standardized tools with subsequent prospective longitudinal follow-up with repeat assessments. The length of a safety PMR assessing neurocognitive effects should be of sufficient length to account for expected neurodevelopmental changes in growing pediatric patients.

IV. Conclusions/Recommendations:

Applicability of the data submitted in NDA 215498 to the U.S. PFIC Population:

- There is no current published literature to suggest that findings of safety and effectiveness of odevixibat use for the treatment of pruritis in PFIC derived from studies in a population outside the U.S. would not be applicable to U.S. PFIC patients.
- Understanding that there is limited enrollment of BSEP1 patients (12 of 45) among the PFIC 2 cohort in Study A4250-005, an analysis of pruritis improvement should be undertaken comparing patients with BSEP 1 and BSEP 2 to ensure there are no obvious differences in efficacy that would suggest clinically meaningful differences between the U.S. and non-U.S. population where the relative proportion of BSEP sub-types may differ.

For assessment of growth in a safety PMR for odevixibat in pediatric patients with PFIC, DPMH has the following recommendations:

- Evaluate whether growth data collected over the 72-week open-label extension trial (Study A4250-008) is sufficient to assess growth as a safety outcome.
- A PMR trial assessing growth should be at least 12 months in duration to allow for adequate and interpretable assessment of growth.
- The primary safety endpoint should focus on assessment of both the absolute change in height/length and changes from baseline in the height/length z-score.
- The Applicant should submit a draft protocol for Agency review and agreement before initiating the trial.
- Protocol level comments to consider include the following:

(b) (4)

(b) (4)

[redacted]

For assessment of neurocognitive outcomes in a safety PMR for odevixibat, DPMH has the following recommendations:.

- Evaluate whether FSV deficiency data collected over the 72-week open-label extension trial (Study A4250-008) is sufficient to address the potential impact of long-term odevixibat treatment on neurocognition in pediatric patients with PFIC.
- A PMR assessing neurocognitive outcomes should include patients 4 years of age and older.
- A PMR assessing neurocognition should be at least 24 months in duration and should account for expected neurodevelopmental changes in growing pediatric patients to allow for adequate and interpretable results.
- Neurocognitive assessments should be performed at a minimum of every 6 months in the study cohort.

(b) (4)

[redacted]

- The Applicant should engage with the Division of Clinical Outcome Assessment early to identify validated neurocognitive measurement tools which could be used to test neurocognitive outcomes across the age range of potential neurodevelopmental susceptibility from odevixibat exposure.
- The Applicant should submit a draft protocol for Agency review and agreement before initiating the trial.
- Protocol level comments to consider include the following:

(b) (4)

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