Statistical Analysis Plan (SAP)

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Revision History

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Final v1.0/20Mar2020	NA	
Final v1.1/11Aug2020	PPD	1. To clarify missing data will not be imputed for analysis. 2. To update dictionary version. 3. To clarify the growth analysis will be based on derived growth data using the software or methods from the Centers for Disease Control and Prevention (CDC) website for patients with age ≥ 2 years old and from the WHO website for patients with age < 2 years old. 4. To clarify the counting of number of adverse events. 5. To clarify that local laboratory data will be used when central laboratory data are not available. 6. To clarify the calculation of change from baseline for AM&PM pruritus scores (daily, weekly, bi-weekly, monthly) for analysis purposes. 7. To update the analysis windows of non-eDiary assessments. 8. To add the analysis windows for the endpoints of eDiary assessments.
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Final v2.1/04Apr2024	PPD	1. To add header sample for final CSR tables. 2. To update endpoints to add the visit during extension period if available. 3. To update the analysis windows for patient entering extension period. 4. To follow the criteria for liver monitoring per protocol amendment 06. 5. To update disposition categories. 6. To update the definition of TEAE by adding "Within 28 days follow-up after the last dose of odevixibat". 7. To update the rule for laboratory related efficacy endpoints to only consider the data up to 14 days follow up after the last dose of odevixibat. 8. To add analysis of change from baseline 1 and 2 for serum bile acid, pruritus, and growth. Baseline 1 is only for odevixibat treated patients in Cohort 1. 9. To add proportion of responders for pruritus scores as secondary endpoint. 10. To add change and shift in use of UDCA and/or Rifampicin at Weeks 24, 48, and 72 in secondary endpoint. 11. To add listing for BRIC patients for episodic flares during the study treatment in exploratory endpoint. 12. To add any possible sequelae of FSV deficiency TEAEs by SOC and PT. 13. To add PT Terms of possible sequelae of FSV deficiency into Appendix G.

Table of Contents

List of Appendices

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
AE(s)	Adverse Event(s)
AFP	Alfa-fetoprotein
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APRI	Aspartate Aminotransferase to Platelet Ratio Index
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BRIC	Benign Recurrent Intrahepatic Cholestasis
CAP	Controlled Attenuation Parameter
CDC	Centers for Disease Control and Prevention
CDF	Cumulative Distribution Function
CI	Confidence Interval
COVID-19	Coronavirus Disease 2019
CPK	Creatine Phosphokinase
CSR	Clinical Study Report
DSMB	Data Safety and Monitoring Board
eCRF	Electronic Case Report Form
eDiary	Electronic Diary
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
Fib-4	Fibrosis-4
GGT	Gamma-glutamyl Transferase
GIC	Global Impression of Change
GIS	Global Impression of Symptoms
ICF	Informed Consent Form

Abbreviation	Definition
ICH	International Council for Harmonisation
INR	international normalised ratio
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
LDH	Lactate Dehydrogenase
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-stage Liver Disease
NA	Not Applicable
NAPPED	Natural Course and Prognosis of PFIC and Effect of biliary Diversion
NDA	New Drug Application
ObsRO	Observer-reported Outcome
p-C4	Plasma 7α-hydroxy-4-cholesten-3-one Concentration
PedsQL	Pediatric Quality of Life Inventory
PELD	Paediatric End-stage Liver Disease
PFIC	Progressive Familial Intrahepatic Cholestasis
PRO	Patient-reported Outcome
PT	Preferred Term
QoL	Quality of Life
RoW	Rest of World
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System Software
SE	Standard Error
SI	International System of Unit
SOC	System Organ Class
StdDev	Standard Deviation
T	Telephone Contact

Abbreviation	Definition
TEAE(s)	Treatment-emergent Adverse Event(s)
TFLs	Tables, Figures, and Listings
ULN	Upper Limit of Normal
US	United States
V	Clinic Visit
VS	Visit Screening
WHO	World Health Organization

1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide detailed descriptions of the statistical methods, data derivations, and data displays for Study Protocol A4250-008, *An Open-Label Extension Study to Evaluate Long-Term Efficacy and Safety of A4250 in Children with Progressive Familial Intrahepatic Cholestasis Types 1 and 2 (PEDFIC 2)*. The table of contents and templates for the tables, figures, and listings (TFLs) will be produced in a separate document.

Any deviations from this SAP will be described and justified in the clinical study report (CSR). The preparation of this SAP has been based on International Council for Harmonisation (ICH) E3 and E9 guidelines[1],[2]. All data analyses and generation of TFLs will be performed using Statistical Analysis System (SAS®) software (Version 9.4 or higher). The SAP will be finalised and signed off prior to locking the database.

2. Study Objectives

2.1 Primary Objectives

Cohort 1

To demonstrate a sustained effect of odevixibat (A4250) on serum bile acids and pruritus in children with progressive familial intrahepatic cholestasis (PFIC) Types 1 and 2.

Cohort 2

To evaluate the effect of odevixibat on serum bile acids and pruritus in patients with PFIC who either (1) Do not meet eligibility criteria for Study A4250-005 (PEDFIC 1) or (2) Patients who do meet the eligibility criteria for Study A4250-005 after recruitment of Study A4250-005 has been completed.

[1] ICH Topic E3: Structure and Content of Clinical Study Reports (CPMP/ICH/137/95- adopted December 1995)

[2] ICH Topic E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96 – adopted March 1998).

2.2 Secondary Objectives

Cohorts 1 and 2:

- To evaluate the long-term safety and tolerability of repeated daily doses of odevixibat
- To evaluate the effect of odevixibat on growth
- To evaluate the effect of odevixibat on biliary diversion and/or liver transplantation
- To evaluate the effect of odevixibat on biochemical markers of cholestasis and liver disease

3. Study Design

3.1 General Study Design

This is a Phase 3, multicentre, open-label extension study to investigate the long-term efficacy and safety of odevixibat at doses of 40 and 120 µg/kg/day in patients with PFIC, including episodic forms also referred to as benign recurrent intrahepatic cholestasis (BRIC). Cohort 1 includes children with PFIC Types 1 and 2 who have participated in Study A4250-005. Cohort 2 includes patients with any type of PFIC who have elevated serum bile acids and cholestatic pruritus and who either (1) did not meet eligibility criteria for Study A4250-005 (PEDFIC 1) or (2) were eligible for enrolment in Study A4250-005 after recruitment of Study A4250-005 completed. Up to 40 patients' post-biliary diversion surgery were allowed to participate in Cohort 2.

Study data are reviewed periodically (approximately on a quarterly basis) by a Data Safety and Monitoring Board (DSMB) until the last patient reaches 72 weeks.

Informed consent must have been obtained before any study procedures were performed. After signing the informed consent form (ICF), patients were evaluated for study eligibility and considered to be enrolled in the study. For Cohort 1, patients were eligible to participate in this extension study if they completed the 24 weeks of treatment in Study A4250-005, or, prior to amendment 6 of the A4250-005 protocol, withdrew from Study A4250-005 after a minimum of 12 weeks of treatment with odevixibat due to

patient/caregiver judgment of no improvement/intolerable symptoms but met all inclusion criteria and no exclusion criteria. Patients who withdrew from Study A4250-005 due to a study drug-related adverse event (AE) were not eligible. For Cohort 2, patients meeting all inclusion criteria and no exclusion criteria were eligible.

Before protocol amendment 6 of the A4250-008 protocol, eligible patients were enrolled into this open-label extension study and treated with a daily dose of odevixibat 120 µg/kg/day for 72 weeks. Patients not tolerating the 120 µg/kg/day dose after a minimum of 1 week had the option to down-titrate to a lower dose (40 µg/kg/day). The patient was to return to the higher dose as soon as deemed appropriate by the investigator. Under protocol amendment 6, patients entering Cohort 2 were to start treatment at 40 µg/kg/day with the possibility to dose escalate to 120 µg/kg/day after 12 weeks if there was no improvement in pruritus based on investigator judgment. The patient could return to the lower dose if the 120 µg/kg/day dose was not tolerated following a minimum of 1 week of treatment. Any dose titration was to be done in consultation with the sponsor Medical Monitor or designee. Patients who wished to continue receiving odevixibat after 72 weeks had the option to remain on treatment in an extension period with visits every 16 weeks until the drug was commercially available, provided continued use was supported by the risk-benefit profile and the patient had not been previously withdrawn or discontinued from the study. In that case the 4-week Follow-up period would not occur.

Patients in Cohort 2 went through a Screening period consisting of 2 clinic visits as follows:

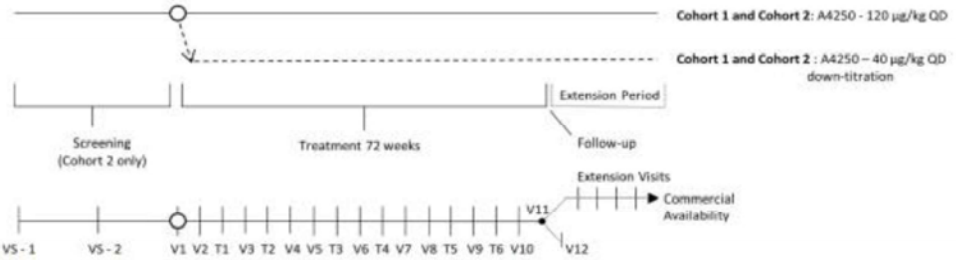
- Visit S-1: Screening Visit 1 (Days -56 to -35)
- Visit S-2: Screening Visit 2 (Days -28 to -7)

Patients who did not meet eligibility criteria may have been re-screened after consultation with the Medical Monitor. Patients not fulfilling inclusion/exclusion criteria after 3 attempts were not allowed to rescreen.

All patients were to have a minimum of 12 clinic visits and 6 scheduled telephone contacts (see Figure 1 and Figure 2) as follows:

- Visit 1: Screening/inclusion visit (Day 1; coincided with Visit 9/End of Treatment (EOT) in Study A4250-005 for patients in Cohort 1. Assessments that were performed at Visit 9/EOT during Study A4250-005 were not to be repeated.)
- Visit 2: Week 4
  − Telephone contact 1: Week 8
- Visit 3: Week 12
  − Telephone contact 2: Week 18
- Visit 4: Week 22
- Visit 5: Week 24
  − Telephone contact 3: Week 30
- Visit 6: Week 36
  − Telephone contact 4: Week 42
- Visit 7: Week 46
- Visit 8: Week 48
  − Telephone contact 5: Week 54
- Visit 9: Week 60
  − Telephone contact 6: Week 66
- Visit 10: Week 70
- Visit 11: Week 72/optional extension period
- Visit 12: Follow-up visit; Week 76 (for those not participating in optional extension period)
- Optional extension period visits every 16 weeks; Week 88 and onwards

Figure 1 Study Design

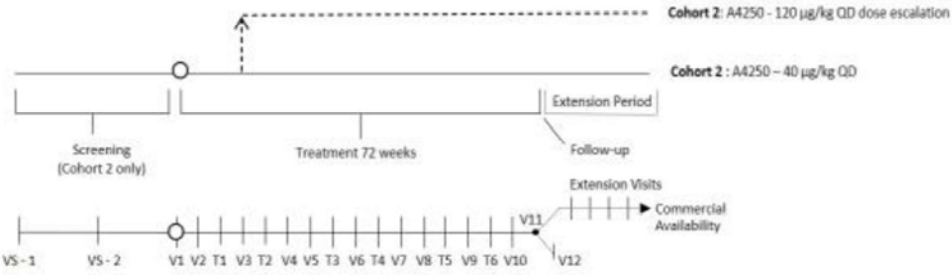


QD: once daily; T: telephone contact; V: study visit; VS: Visit Screening

Note: Visit 1 coincides with Visit 9 of Study A4250-005. Patients who are not tolerating the 120 µg/kg/day dose may be down-titrated to the 40 µg/kg/day dose following a minimum of 1 week of treatment. The patient can return to the higher dose as soon as deemed appropriate.

This figure is only applicable to Cohort 2 up to Protocol Amendment 5. Figure 2 presents the study design for Cohort 2 as of Protocol Amendment 6.

Figure 2 Study Design for Cohort 2 as of Protocol Amendment 6



QD: once daily; T: telephone contact; V: study visit; VS: Visit Screening

Note: As of Protocol Amendment 6, patients entering Cohort 2 will start treatment at 40 µg/kg/day with the possibility to dose escalate to 120 µg/kg/day after 12 weeks if there is no improvement in pruritus based on investigator judgment. The patient can return to the lower dose if the 120 µg/kg/day dose is not tolerated following a minimum of 1 week of treatment.

Patients were to return to the clinic at Weeks 4 and 12 and thereafter every 10 to 12 weeks for follow-up measurements. Between clinic visits there was to be a telephone contact with the patient and/or caregiver to report AEs. Additional clinic visits may have been required for patients who needed direct site assistance for AE monitoring for safety maintenance and other assessments.

At Visit 11, patients were to be offered the choice to continue receiving odevixibat treatment in an optional extension period. During the optional extension period the patient was to receive odevixibat at the same dose as at the end of the 72-week treatment

period, returning to the clinic every 16 weeks until the drug is commercially available, provided continued use was supported by the risk-benefit profile and the patient had not been previously withdrawn or discontinued from study.

If a patient was prematurely withdrawn from the study prior to Week 72, all assessments scheduled for Visit 11 were to be performed at the time the patient withdrew. If a patient participating in the optional extension study withdrew prior to commercial drug availability, all assessments scheduled for the optional extension period EOT visit were to be performed.

If a liver biopsy was performed according to the local regulations or standard of care at any time during A4250-008, the biopsy results should have been recorded in the electronic case report form (eCRF). If liver biopsy results were collected for a patient in Study A4250-005 or prior to Week 24 in Study A4250-008, the patient was to be asked to consent to a follow-up liver biopsy at Visit 11, if allowed per local regulations, unless 2 prior liver biopsy results had been collected (with at least 1 year between biopsies). Liver biopsies were not performed in Spain.

For patients not participating in the optional extension period, Visit 12 was to take place 28 days after Visit 11. All patients who were prematurely withdrawn were to have this visit 28 days after the last dose of study drug for AE monitoring and other safety follow-up assessments.

If a patient discontinued before Week 72, additional telephone contacts were to be made every 3 months after the Follow-up visit (Visit 12) up to Week 72 to inquire whether the patient had undergone biliary diversion or liver transplantation, and if ongoing TEAEs at the time of discontinuation had resolved. The telephone calls were to take place up until 72 weeks even if the patient had biliary diversion or liver transplant.

Patients and/or caregivers were instructed to complete the electronic diary (eDiary) every morning and evening for the first 24 weeks (Visits 1 to 5) and for the 21 days before each clinic visit thereafter (Visits 6 to 12). In addition, Cohort 2 patients and/or caregivers were instructed to complete the eDiary during the Screening period. Patients participating in the optional extension period were not to complete eDiary entries after Visit 11. The eDiary included patient-reported outcome (PRO) and observer reported outcome (ObsRO) items for evaluation of itching (using PRO), scratching (using ObsRO), and

sleep disturbance (using both PRO and ObsRO). ObsRO in patients of all ages was recorded by a caregiver. If possible, the same caregiver was to complete the ObsRO items throughout the study. Additionally, caregivers were requested to report in the diary the time that study drug was administered during the treatment period.

The study nurse was to monitor eDiary compliance by routine review of the CRF Health website. If both diary entries were missing on a specific day during this time, the study nurse was to call the caregiver/patient with a reminder to complete all scheduled entries. Non-compliance was to be documented and explained in the source documents.

3.2 Randomisation and Blinding

Not applicable (NA).

3.3 Study Treatments and Assessments

Prior to Amendment 6 of the protocol, all patients were dosed with 120 µg/kg/day for 72 weeks. As of Amendment 6, patients enrolled in Cohort 2 received 40 µg/kg/day for at least the first 12 weeks with the option to increase the dose to 120 µg/kg/day for the remaining 60 weeks if there was no improvement in pruritus based on investigator judgement. Patients not tolerating the 120 µg/kg/day dose after a minimum of 1 week for reasons other than new liver findings and severe diarrhoea had the option to down-titrate to a lower dose (40 µg/kg/day). They were to return to the higher dose as soon as deemed appropriate by the Investigator. More than one upward dose titration (from 40 µg/kg/day directly to 120 µg/kg/day) for the same event was not recommended. If, in the opinion of the Investigator, a dose titration should be considered prior to the 1-week minimum, the Investigator was to consult with the Medical Monitor or designee. Any dose titration should have been done in consultation with the Sponsor Medical Monitor or designee.

Study drug was to be dispensed to the patient at defined intervals from Visit 1 through Visit 9, together with instructions on how to store and take the drug. Study drug administration data, including whether each patient took each dose or partial doses of study drug, whether there were any delayed or missed doses, and whether the capsule was opened or swallowed whole, was to be documented through the diaries and transferred to the study database.

Patients participating in the optional extension period were to continue at the same dose as at the end of the 72-week treatment period (120 µg/kg/day or 40 µg/kg/day). Patients not tolerating the dose at any time throughout the extension period were to have the option to down-titrate to a lower dose (40 µg/kg/day) following consultation with the Sponsor Medical Monitor or designee. Patients were to return to the higher dose as soon as deemed appropriate by the Investigator. More than one upward dose titration (from 40 µg/kg/day directly to 120 µg/kg/day) for the same event was not recommended.

Bottles with 34 capsules were to be given to the patient at each visit. A patient who required 2 or more capsules per day was to be given multiple bottles; please refer to the investigational product manual. If a patient's weight changed at any time during the study, dose adjustment was required. The number of capsules provided to the patient was to be based on the body weight thresholds identified in Protocol A4250-008, Table 3.

Odevixibat was to be taken in the morning together with food. On clinic visits days when laboratory assessments were conducted (Visits 1 to 10; and every 16 weeks thereafter for those participating in the optional extension period), study drug was to be taken after the visit.

Efficacy assessments and daily recording of pruritus using an eDiary in this study are briefly introduced as follows.

3.3.1 Serum Bile Acids

Blood samples for analysis of fasting total serum bile acids were to be drawn at all visits from Visit 1 (Visit S-1 for Cohort 2) through Visit 12. Fasting serum bile acids were also to be drawn at all visits (every 16 weeks) during the optional extension period. Patients were to fast (water intake only) for at least 4 hours prior to the collection of samples for serum bile acids. Exceptions could be made for infants <12 months of age if unable to fast for the full 4 hours. For any visit at which a bile acid sample result was unreportable, an additional unscheduled visit for a repeat sample collection may have been scheduled. Samples were to be handled and transported to a central laboratory per instructions in the laboratory manual.

3.3.2 Itching, Scratching, and Sleep Score

Itching, observed scratching, and sleep disturbance were to be recorded twice each day via the eDiary. Patient and/or caregivers were instructed to fill in the eDiary every morning (AM score representing nighttime itching/scratching and sleep disturbance) and evening (PM score representing daytime itching/scratching and tiredness) for the first 24 weeks and the last 21 days before all the remaining visits to the clinic. There was to be no interruption between Visits 11 and 12. Patients participating in the optional extension period stopped eDiary entries at Visit 11. Patients and/or caregivers were instructed to complete the eDiary in the morning after the patient awakened and in the evening just before the patient went to sleep.

The eDiary includes Albireo ObsRO and PRO items. Patients <8 years of age were not asked to complete the Albireo PRO items; the Albireo ObsRO was to be completed by caregivers of patients in this age group. Older patients, ≥ 8 years of age, completed the Albireo PRO items and the caregiver completed the Albireo ObsRO items. The Albireo PRO items assess severity of itch, aspects of sleep disturbance (morning diary only), and tiredness. For patients 8 to 12 years of age, the caregiver read the Albireo PRO items along with the child and recorded the child's response. A guide was provided to the caregivers that provided standardised explanations of the Albireo PRO items, in case the patient was confused or required clarification about the meaning of a question. The Albireo ObsRO items assess severity of observed scratching, aspects of observed sleep disturbance (morning diary only), and observed signs of tiredness (evening diary only). The Albireo ObsRO and PRO scratching and itch severity items use 0 to 4 response scales, where each response is distinguished by a unique facial expression, verbal anchor, number, and colour code.

3.3.3 Growth

Prior to Amendment 6 of the protocol, standard height measurements were obtained, and weight was evaluated using a certified weight scale. As of Amendment 6, growth (height and weight) was to be measured by the standardized assessments outlined in the US FDA guidance document, Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children (March 2007). Height and length (velocity) was to be

measured using a certified stadiometer and weight (Z-score) using a certified weight scale.

Mid-arm circumference (3 repeat measurements) was to be collected at the study site for all patients after Protocol Amendment 6.

Study sites were trained on using a standardized approach when measuring height with a stadiometer and additional detailed instructions were provided in study documents.

BMI was calculated by weight (kg) / height $(m)^2$. Change was defined as linear growth deficit (weight and BMI for age) compared to a standard growth curve.

3.3.4 Biomarker Sample

Blood samples for plasma 7α-hydroxy-4-cholesten-3-one concentration (p-C4) and autotaxin were to be drawn at Visits 1, 2, 5, 8, and 11 for patients with body weight >10 kg. Samples were to be handled and transported to a central laboratory per instructions in the laboratory manual.

3.3.5 Change of Antipruritic Medication

Any change of antipruritic medication must be noted in the eCRF.

3.3.6 Quality of Life Questionnaire (PedsQL)

Patients and caregivers were asked to complete a quality of life (QoL) questionnaire, the Pediatric Quality of Life Inventory (PedsQL), at Visits 1, 5, 8, 11 and at all visits of the optional extension period. Details of the questions included on the questionnaire are located in Appendix 4 of the protocol.

3.3.7 PELD/MELD Score

The paediatric end-stage liver disease (PELD) score was calculated for children under 12 years of age. For children 12 years of age or older, the model for end-stage liver disease (MELD) score was calculated.

For calculation of the PELD/MELD score[3] laboratory parameters will be converted in following units:

- Total bilirubin in mg/dL
- Albumin in g/dL
- Creatinine in mg/dL

PELD score = 4.80 * ln(total bilirubin) + 18.57 * ln(INR) - 6.87 * ln(albumin) + 4.36 (if patient <1 year: scores for patients listed for liver transplantation before the patient's first birthday continue to include the value assigned for age (<1 year) until the patient reaches the age of 24 months) + 6.67 (if the patient has growth failure [< -2 StdDev])

Laboratory values <1.0 were set to 1.0 for the calculation of the PELD score.

MELD score = 9.57 * ln(creatinine) + 3.78 * ln(total bilirubin) + 11.2 * ln(INR) + 6.43

Laboratory values <1.0 were set to 1.0 and serum creatinine values >4.0 mg/dL (equivalent of 353.6 µmol/L) were set to 4.0 for calculation of the MELD score.

If a patient went from 11 years of age to 12 between the beginning and end of study, both PELD and MELD scores were to be calculated at the first visit after the 12th birthday and move to MELD score.

3.3.8 Fibroscan®

Where available, Fibroscan® was to be performed as per institution standard practice at Visits 1, 5, 8, and 11. The data collected on the Fibroscan form (liver stiffness measured in kPa and controlled attenuation parameter (CAP) measured in dB/m) was to be

[3] https://www.unos.org/wp-content/uploads/unos/MELD_PELD_Calculator_Documentation.pdf; accessed on 25-Jul-2018.

converted to determine stage of fibrosis and grade of steatosis, respectively, using a score card[4,5] as outlined in Table 1 and Table 2.

Table 1: Fibroscan Scoring for Cholestatic Liver Disease (Fibrosis Score)

Score	F0 to F1 No Scarring/ Mild Fibrosis	F2 Moderate Fibrosis	F3 Severe Fibrosis	F4 Cirrhosis or Advanced Fibrosis
Fibroscan result	2 to 7 kPa	>7 to 9 kPa	>9 to 17 kPa	>17 kPa

Table 2: Controlled Attenuation Parameter Score and Steatosis Grading

Controlled Attenuation Parameter Score	Amount of Liver with Fatty Change	Steatosis Grade
<238 dB/m	–	S0
238 to 260 dB/m	11% to 33%	S1
260 to 290 dB/m	34% to 66%	S2
>290 dB/m	≥67%	S3

3.3.9 Markers of Fibrosis

Aspartate aminotransferase to platelet ratio index (APRI) score and fibrosis-4 (Fib-4) score were calculated at Visits 1, 3, 5, 8, and 11.

APRI = [(AST in U/L)/(AST upper limited of normal (ULN) in U/L)] × 100/(platelets in 10^9/L)

Fib-4 score = (age*AST in U/L)/(platelets in 10^9/L * √ (ALT in U/L)).

3.3.10 Liver Biopsy

If a liver biopsy was performed according to the local regulations or standard of care at any time during Study A4250-008, the biopsy results should have been recorded in the

[4] Understanding your Fibroscan Results. Memorial Sloan-Kettering Cancer Center Web site. https://www.mskcc.org/cancer-care/patient-education/understanding-your-fibroscan-results Updated February 27, 2018. Accessed March 27, 2020.

[5] Jewish Hospital Fibroscan Interpretation Assessment SOP. Washington University, Louisville Kentucky. https://louisville.edu/medicine/departments/medicine/divisions/gimedicine/physician-resources/calculators-and-tools-files/fibroscan-interpretation-sheet. Undated.

eCRF. If the patient had liver biopsy results collected in Study A4250-005 or prior to Week 24 in Study A4250-008, the patient was to be asked to consent to a follow-up liver biopsy, if allowed per local regulations, at Visit 11 unless 2 prior liver biopsy results had been collected with at least one year between biopsies. Liver biopsies were not performed in Spain.

3.3.11 Global Impression of Change and Global Impression of Symptom Measures

Patients, caregivers, and clinicians were to complete the global impression of change (GIC) and the global impression of symptom (GIS) measures at Visits 1, 2, 3, 5, 8, and 11, and at all visits during the optional extension period.

The GIC items assess change in itch (patient version), scratching (caregiver and clinician versions), and sleep (all versions) since starting the study drug. The GIS items assess itch (patient version), scratching (caregiver and clinician versions), and sleep (all versions) in the past week. Caregivers and clinicians were to complete the GIC and GIS for all patients; only patients ≥8 years of age were to complete the patient version.

A detailed description of procedures and assessments to be conducted during this study is summarised in the Table 1 Schedule of Assessments (Screening Period through Follow-up Period) and Table 2 schedule of study assessments (Optional Extension Period) of the protocol.

4. Study Endpoints

4.1 Primary Efficacy Endpoints

The primary efficacy endpoints are as follows:

- **EU and Rest of the World (RoW):** Change from baseline in fasting serum bile acids after 72 weeks of treatment.

  Change from baseline will be calculated based on the average of the values at Weeks 70 and 72. The baseline fasting serum bile acids value is defined as follows unless otherwise specified:

Cohort 1: The average of the last 2 values before the first dose of study drug in Study A4250-008. In general, these 2 values are the values of the last 2 assessments of Study A4250-005. If pre-dose assessments are collected in Study A4250-008 for a patient, then the values of pre-dose assessments in Study A4250-008 will be considered first and used to calculate the baseline. These 2 values need to be taken from 2 consecutive scheduled visits or unscheduled visits. If only one value is available from 2 consecutive scheduled visits or unscheduled visits, then that value will be used as baseline.

Cohort 2: The average of the last 2 values before the first dose of study drug in Study A4250-008.

- **United States (US):** Proportion of positive pruritus assessments at the patient level over the 72-week treatment period using the Albireo ObsRO instrument.

  A positive pruritus assessment is defined as a scratching score of ≤1 or at least a one-point decrease from baseline on the Albireo ObsRO instrument. At each assessment, the AM score will be compared to the baseline AM average, and the PM score will be compared to the baseline PM average. Both AM and PM pruritus assessments will be included in the analysis of this endpoint. AM scores from the period of 14 days before or on the first dose day in Study A4250-008 will be averaged as the AM baseline. PM scores from the period of 14 days before the first dose day in Study A4250-008 will be averaged as the PM baseline. If a patient's baseline average score is ≤ 1, then only the criterion of a one-point drop from baseline on the Albireo ObsRO instrument will be used to determine whether a pruritus assessment is positive or not for the primary endpoint analysis.

4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include the following:

- **EU and RoW:** Proportion of positive pruritus assessments at the patient level over the 72-week treatment period using the Albireo ObsRO instrument.
- **US:** Change from baseline in fasting serum bile acids after 72 weeks of treatment.
- **All Regions:**

- Change from baseline in serum bile acids at Weeks 4, 12, 22, 24, 36, 46, 48, 60, 70, 72, 76 and all visits (every 16 weeks) during the optional extension period.
- Proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument from Weeks 0-4, Weeks 0-12, Weeks 0-22, Weeks 0-24, Weeks 0-36, Weeks 0-46, Weeks 0-48, Weeks 0-60, and Weeks 0-70, and the proportion of positive pruritus assessments at each 4--week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between Visit 5/Week 24 and Visit 12/Week 76.
- Proportion of individual AM assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument from Weeks 0-4, Weeks 0-12, Weeks 0-22, Weeks 0-24, Weeks 0-36, Weeks 0-46, Weeks 0-48, Weeks 0-60, Weeks 0-70, and Weeks 0-72, and the proportion of positive pruritus assessments at each 4-week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between Visit 5/Week 24 and Visit 12/Week 76.
- Proportion of individual PM assessments meeting the definition of a positive pruritus assessment at the patient level using the Albireo ObsRO instrument from Weeks 0-4, Weeks 0-12, Weeks 0-22, Weeks 0-24, Weeks 0-36, Weeks 0-46, Weeks 0-48, Weeks 0-60, Weeks 0-70, and Weeks 0-72, and the proportion of positive pruritus assessments at each 4-week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between Visit 5/Week 24 and Visit 12/Week 76.
- Number of patients undergoing biliary diversion surgery or liver transplantation. These parameters will be evaluated separately and together at Weeks 24, 48, 72 and all visits (every 16 weeks) during the optional extension period.
- Change in growth from baseline to Weeks 12, 24, 36, 48, 60, 72 and all visits (every 16 weeks) during the optional extension period after initiation of odevixibat treatment, defined as the linear growth deficit (height/length

for age, weight for age, and BMI) compared to a standard growth curve (Z-score, StdDev from the fiftieth percentile, P50).

- Change in APRI score and Fib-4 score from baseline to Week 72 and all visits (every 16 weeks) during the optional extension period.
- Change in PELD/MELD score from baseline to Week 72 and all visits (every 16 weeks) during the optional extension period.
- Change in use of UDCA and/or Rifampicin at Weeks 24, 48, and 72.
- Proportion of responders for pruritus scores using the Albireo ObsRO instruments by visit (proportion of patients achieving meaningful reduction based on the clinically meaningful threshold of 1.0 point, which is estimated from the distribution-based and anchor-based approaches in the blinded psychometric analysis)

4.3 Exploratory Endpoints

All Exploratory Endpoints will be evaluated at Weeks 24, 48, and 72 unless otherwise noted. For summary purposes, if not otherwise specified, the baseline value of a parameter is defined as the last non-missing assessment of that parameter before the first dose of odevixibat in Study A4250-008. Exploratory efficacy endpoints include the following:

- Change in serum alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT), and total bilirubin concentration from baseline to Week 72 and all visits (every 16 weeks) during the optional extension period.
- Proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level over the 72-week treatment period. A positive pruritus assessment includes an itch score ≤1, or at least a 1 -point decrease from baseline based on the Albireo PRO instrument; only patients ≥8 years of age will complete the Albireo PRO instrument.
- Change from baseline in sleep parameters by each 4-week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between

Visit 5/Week 24 and Visit 11/Week 72 over the 72-week treatment period measured with the Albireo PRO and ObsRO instruments.

- Change from baseline in international normalised ratio (INR), albumin, liver enzymes, leukocytes, and platelets from baseline to Week 72 and all visits (every 16 weeks) during the optional extension period.
- Change from baseline to all visits where assessed in measures of bile acid synthesis (autotaxin, p-C4)
- Assessment of global symptom relief at Weeks 4, 12, 24, 48, 72 and all visits (every 16 weeks) during the optional extension period as measured by patient, caregiver, and clinician GIC items.
- Change from baseline by each 4-week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between Visit 5/Week 24 and Visit 12/Week 76 in patient-reported and observer-reported night-time itching and scratching severity scores.
- Change from baseline by week interval from Baseline to Week 72 in patient-reported and observer-reported night-time itching and scratching severity scores.
- Change from baseline by each 4-week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between Visit 5/Week 24 and Visit 12/Week 76 in patient-reported and observer-reported morning time itching and scratching severity scores.
- Change from baseline by week interval from Baseline to Week 72 in observer-reported morning time itching and scratching severity scores.
- Change from baseline by each 4-week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between Visit 5/Week 24 and Visit 12/Week 76 in pooled pruritus score including observer-reported scratching for patients <8 years of age and patient-reported itch severity for patients ≥8 years of age.

- Change from baseline by week interval from Baseline to Week 72 in pooled pruritus score including observer-reported scratching for patients <8 years of age and patient-reported itch severity for patients ≥8 years of age.
- Change from baseline in additional patient-reported and observer-reported sleep parameters (e.g. tiredness, number of awakenings) by each 4-week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between Visit 5/Week 24 and Visit 12/Week 76.
- Change from baseline in PedsQL questionnaire from Baseline to Week 72 and all visits (every 16 weeks) during the optional extension period.
- Change from baseline in stage of liver fibrosis as assessed by Fibroscan® (where available).
- Change from baseline in stage of liver fibrosis, as assessed by post-treatment biopsy (when available).

4.4 Safety Evaluation

Safety criteria are as follows:

- The primary safety analysis for this study will include the incidence of total treatment-emergent adverse events (TEAEs) and TEAEs categorised by causality, severity, and seriousness assessments made by the Investigator.
- Trends in safety will also be evaluated for the following:
  - Physical examinations
  - Concomitant medications
  - Vital signs
  - Laboratory test results (including clinical chemistry, haematology, urinalysis, alfa-fetoprotein [AFP], vitamins A and E, 25-hydroxy vitamin D, and INR)
  - Abdominal ultrasound
  - Discontinuations due to AEs

5. Sample Size and Power

There is no formal hypothesis testing in this open-label study. The sample size for Cohort 1 was determined in Study A4250-005. For Cohort 1, patients will be enrolled after completion of Study A4250-005 or participation of 12 weeks in that study. For the other endpoints, mainly descriptive analyses will be performed.

The proportion of patients with at least 1 event (i.e., surgical bile diversion, liver transplantation, death) that can be expected in a non-treated population depends on PFIC type and age distribution of the included patients. The expected proportion of patients with events will be calculated for the study population once each patient's age and PFIC type are known, using the probability that a patient will get an event estimated from the reference population in the ongoing observational cohort study, NAtural Course and Prognosis of PFIC and Effect of Biliary Diversion (NAPPED).

As an example, if the expected proportion of patients with at least 1 event is estimated to be 30% in the study population, and then if the proportion of patients with at least 1 event during odevixibat long-term treatment is shown to be only 10% in the study, the power is approximately 89% to 96% (1-sided test, alpha=2.5%) for a confidence interval (CI) with upper boundary <30% based on a sample size of n=48 to 60. The sample size of 60 for Cohort 2 was estimated based on the availability of target patient population to evaluate the therapeutic benefit for those patients.

6. Interim Analysis

This study is an extension study of Study A4250-005 and was ongoing at the time of the New Drug Application (NDA) and Marketing Authorisation Application (MAA) submission in November 2020. For the NDA/MAA submission purposes, the database was locked on 31Aug2020 for Study A4250-005, and an interim analysis of Study A4250-008 with data cut on 15Jul 2020 was performed to accompany the final analyses of Study A4250-005.

For this interim analysis submitted in the NDA/MAA, the analyses described in this SAP were conducted, as appropriate, based on data available at the time of the data cut-off date. The interim analysis was conducted for both safety and efficacy mainly based on descriptive statistics. The main time point was at the end of 24-week treatment period

while all data were included for by-visit summaries. These analyses accompanied the Study A4250-005 analyses and provided further information regarding the safety and efficacy of odevixibat dosing for more than 24 weeks.

For supporting a post-marketing commitment, an interim analysis of Study A4250-008 (planned data cut of 31July2022) was performed in order to update the CSR. The selected analyses described in this SAP were conducted, as appropriate, for the interim analysis based on data available at the time of the data cut-off date. The interim analysis was conducted for both safety and efficacy mainly based on descriptive statistics.

Analyses may be performed at select time points throughout the collection of patient data for regulatory requirements and sponsor decision making purposes.

7. Analysis Sets

The FAS will consist of all patients who received at least 1 dose of study drug in Study A4250-008. The FAS will be the primary analysis set for all analyses unless otherwise specified.

8. Statistical Considerations and Analysis

8.1 Handling of Missing Data and/or Invalid Data and Outliers

8.1.1 Missing Data Analysis Methods for Efficacy Endpoints

No imputation will be made for any missing data. The assessments after intercurrent events (death, or initiation of rescue treatments such as biliary diversion surgery or liver transplantation) or follow-up assessments (≥ last dose day + 15 days) will be excluded from analysis with the exception of the analysis of patients undergoing biliary diversion surgery or liver transplantation. For eDiary data analysis, data after last dose will be excluded from analysis.

9. Statistical Methods

9.1 General Statistical Conventions

Study data will be reviewed periodically (approximately on a quarterly basis) by a DSMB. For DSMB analyses, the Adjudication Process Document outlines the events that

will be adjudicated and see Section 9.8.2. Descriptive statistics are mainly used in this open-label extension study unless otherwise specified. All statistical procedures will be completed using SAS®, Version 9.4 or higher.

Continuous variables will be summarised using descriptive statistics, including the number of patients with non-missing value (n), mean, median, StdDev (or standard error [SE]), minimum, and maximum. The letter "n" will be presented without a decimal point. Minimum and maximum values will be presented to the same precision as in the database. Mean and median will be presented to 1 more decimal place than the minimum and maximum. StdDev or SE will be presented to 1 more decimal place than the mean and median.

For categorical variables, summaries will include counts of patients (frequencies) and percentages. Percentages will be rounded to 1 decimal place. Descriptive summaries of change from baseline in categorical variables will be provided using shift tables, as applicable.

For summary purposes, if not otherwise specified, the baseline value of a parameter is defined as the last non-missing assessment of that parameter before the first dose of odevixibat in Study A4250-008 (Appendix A). Derived variables used for the analyses are provided in Appendix A.

Analysis windows defined in Appendix B will be applied for all laboratory parameters, questionnaires, vital sign measurements, physical examinations, and other efficacy parameters in the study, unless otherwise specified.

For the final CSR, all summaries will be presented for the following treatment groups, unless otherwise specified.

- Placebo (A4250-005) to Odevixibat (A4250-008)
- Odevixibat 40 or 120 µg/kg/day (A4250-005) to Odevixibat 120 µg/kg/day (A4250-008)
- Cohort 2 (A4250-008)
- Odevixibat Overall

Table header will be presented as follows:

Placebo/Odevixibat[a] (A4250-005/A4250-008)	Odevixibat/Odevixibat[b] (A4250-005/A4250-008)	Cohort 2[c] (A4250-008)	Odevixibat Overall

a Includes patients who received placebo in Study A4250-005 and transitioned to odevixibat 120 µg/kg/day in Study A4250-008

b Includes patients who received odevixibat 40 or 120 µg/kg/day in Study A4250-005 and transitioned to odevixibat 120 µg/kg/day in Study A4250-008

c Includes patients who received odevixibat in Cohort 2 of Study A4250-008

All patient data, including derived data, will be presented in individual patient data listings. All listings will be sorted by cohort/treatment subgroup, patient number, date/time, and visit. The sex and age for each patient will be stated on each listing. Data listings will be based on all enrolled patients.

Patients who didn't directly rollover from Study A4250-005 but enrolled in Study A4250-008 after a gap in dosing or re-enrolled in Study A4250-008 after a gap in dosing were assigned separate patient IDs. They will be considered as separate patients in all analyses.

9.2 Patient Disposition

All patients who provided informed consent will be included in a summary of patient accountability.

The following categories will be summarised by cohort/treatment subgroup and overall as follows:

- Patients screened
- Screening failures
- Patients eligible to receive dose
- Patients dosed
- Patients completing 72 weeks treatment period
    - Patients not enrolled in optional extension treatment period
    - Patients enrolled in the optional extension treatment period
        - Patients ongoing in optional extension treatment period

  - Patients discontinuing optional extension treatment period (including reasons for treatment discontinuation)

- Patients discontinuing 72 weeks treatment period early (including reasons for treatment discontinuation)
- Patients who have undergone biliary diversion surgery
- Patients who have undergone liver transplantation
- Patients who have been listed for liver transplantation

Additionally, analysis populations will be summarised overall and by region (Appendix C).

9.3 Protocol Deviations

All protocol deviations will be reviewed at the final protocol deviations review meeting before final database lock, through clinical input provided by the Sponsor, using the following sources of information:

- Protocol deviation logs, provided by ICON Clinical, Pharmacovigilance, Medical, and Data Management.

Important protocol deviations that are likely to impact the efficacy and safety will be identified by the study team during the manual review at the data review meeting prior to DB lock. The list of important protocol deviations will be finalized after the data review meeting. The number of patients with important protocol deviations (overall and by deviation) will be summarised by cohort/treatment subgroup and overall.

9.4 Demographic and Baseline Characteristics

9.4.1 Demographic Characteristics

Age, height, weight, and BMI at baseline and other demographic variables, e.g. age category (<6 months, 6 months to 5 years, 6 to 12 years, 13 to 18 years, and >18 years), sex, race, ethnicity, country, region (Appendix C) will be summarised descriptively by cohort/treatment subgroup and overall.

Demographics data for Cohort 1 will be obtained from Study A4250-005, as appropriate.

9.4.2 Baseline and Disease Characteristics

The following disease characteristics will be summarised by cohort/treatment subgroup and overall: years since PFIC diagnosis; type of PFIC; Bile Salt Export Pump (BSEP) subtype for PFIC 2 Patients and BSEP genotype; presence of significant pruritus per Investigator report; at least 1 serum bile acid level >100 µmol/L within 6 months before Screening visit; serum bile acid category; reasons for discontinuation of historical PFIC-related investigational medications; baseline Z-score; Use of UDCA or/and Rifampicin and diagnostic genetic laboratory test as well as Child-Pugh classification and hepatic impairment classification per NCI Organ Dysfunction Working Group.

Child-Pugh classification: mild (Class A), moderate (Class B), or severe hepatic impairment (Class C) is based on the FDA Guidance for Pharmacokinetics in Patients with Impaired Hepatic Function. Determination of the classification is made based on medical review of baseline laboratory data and medical history.

Hepatic impairment will also be classified per the NCI Organ Dysfunction Working Group classification as mild, moderate or severe (Mansfield et al. 2016)[6]. Both the Child-Pugh and NCI classification will be included in the baseline characteristics and both will be applied in the subgroup analysis based on hepatic impairment status.

The following continuous parameters will also be summarized: estimated glomerular filtration rate (eGFR); baseline Z-score (weight, height, BMI and mid-arm circumference); and baseline values of alanine aminotransferase (ALT); aspartate aminotransferase (AST); gamma-glutamyl transferase (GGT); total bilirubin; alkaline phosphatase; INR; and vitamins A, E, and 25 hydroxy D.

eGFR will be calculated based on the modified/bedside Schwartz equation. For patients <18 year of age, Bedside Schwartz Equation will be used:

GFR (mL/min/1.73 m²) = (36.2 × Height in cm) / Creatinine in µmol/L

For patients ≥ 18 years, the isotope dilution mass spectrometry (IDMS)-traceable Modification of Diet in Renal Disease (MDRD) Study equation will be used:

[6] Aaron S. Mansfield, Michelle A. Rudek, Diana Vulih, Gary L. Smith, Pamela Jo Harris, and S. Percy Ivy (2016). "The effect of hepatic impairment on outcomes in phase 1 clinical trials in cancer subjects".

GFR (mL/min/1.73 m^2) = 175 × (Creatinine in µmol/L/88.4)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 if African American)

The average of three repeat measurements of mid-arm circumference will be calculated for the analyses.

If length instead of height is measured for patients, height of the patients will be calculated from length by using the formula:

Height (cm) = Length (cm) – 0.7 cm.

A listing will present demographic and baseline characteristics by patient. In addition, an individual listing of liver biopsy results, including historical liver biopsy results for patients in Cohort 2, will be produced.

The results of pathologic variants identified for ATP8B1, ABCB11, ABCB4, or other genes (such as NR1H4, TJP2, DCDC2, CLDN1, MYO5B) will be listed for all patients.

9.4.3 Medical and Surgical History

The frequencies and percentages of patients with reported medical and surgical history will be presented by system organ class (SOC) and preferred term (PT). Medical and surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 26.0 or later. The summary table will be sorted alphabetically by SOC and PT. Medical and surgical history will also be listed.

For patients with BRIC, a flare/cholestatic episode can be self-reported or clinically assessed based on medical history. The frequency, duration, and severity of flares within the last 6 months at a minimum, and within the last 5 years, other clinical signs and symptoms during a cholestatic episode/flare including nausea, vomiting and pruritus followed by jaundice, fatigue, weight loss, malaise, steatorrhoea, night blindness, increased bilirubin and alkaline phosphatase levels and increased INR, ALT, AST and GGT, if possible, will be listed.

9.4.4 Prior and Concomitant Medications

Prior and concomitant medications used in this study will be coded using the March 2023 version or later of the World Health Organisation (WHO) Drug Global Dictionary.

Prior medication: A medication taken by a patient within 3 months before the first dose date of study drug with a recorded medication stop date before the first dose date of study drug is a prior medication. This will not include historical PFIC-related investigational medications collected separately on CRFs.

Concomitant medication: A medication taken by a patient the day on or after the first dose date of study drug or a medication with a start date before the first dose date of study drug without a recorded stop date before the first dose date of study drug is a concomitant medication.

As patients in Cohort 1 enter the study directly from Study A4250-005, the summary of prior medications is provided only for Cohort 2. Concomitant medication use during the study will be summarised descriptively using frequency tables by Anatomical Therapeutic Chemical (ATC) Class 4 and PT by cohort/treatment subgroup and overall for the FAS. ATC class and PT will be presented alphabetically. All prior and concomitant medications will be listed. Details for imputing missing or partial start and/or stop dates of non-study medications are located in Appendix D.

9.5 Extent of Exposure

9.5.1 Treatment Duration

Exposure will be summarised with descriptive statistics (n, mean, StdDev, minimum, median, and maximum) and presented by cohort/treatment subgroup and overall.

For Cohort 2 patients who dose escalate from 40 µg/kg/day to 120 µg/kg/day, exposure at each dose and overall will be calculated.

Categorical summaries of treatment duration will also be provided. Study drug exposure will be derived as follows:

Duration of exposure (in weeks) = (date of last study drug intake – date of first study drug intake + 1)/7.

Investigators are allowed to interrupt the study drug to allow for the resolution of AEs, if necessary. Drug interruptions will not be considered when calculating treatment duration.

9.5.2 Treatment Compliance

Treatment compliance will be assessed by maintaining adequate study drug dispensing records. Treatment compliance over the treatment period will be calculated using 2 sources of data.

9.5.2.1 Source Data from CRFs

Treatment compliance = 100 × [(number of capsules dispensed – number of capsules returned)/number of capsules that should have been taken].

The number of capsules that should have been taken is calculated as the number of days that patient was in the treatment period (exposure as above) multiplied by the number of prescribed capsules to be taken (based on patient's body weight, Protocol Table 3) during the treatment period. The total number of capsules actually taken is the total number of capsules recorded as taken based on the CRF (number of capsules dispensed minus returned) summed over the treatment period. If the number of capsules returned is confirmed as missing and the study drug is confirmed has not been returned, the derivation will not be done.

9.5.2.2 Source Data from eDiary

Treatment compliance =100 × (total number of capsules taken/total number of capsules planned to be taken). The number of capsules planned to be taken will be estimated based on patient's body weight per Protocol Table 3. The compliance rate based on eDiary data will be calculated during the first 24 weeks only.

The calculated compliance rates will be summarised and the one based on CRFs will be considered the primary compliance rate. The compliance rates reported by visit on the CRFs also will be summarised.

Descriptive summary statistics will be used to summarise study drug compliance by cohort and overall. The number and percentage of patients with a compliance <80%, between 80% and 120%, and >120% will also be presented.

9.6 Efficacy Analyses

This section addresses the analyses to be conducted on the primary, secondary, and exploratory efficacy variables.

The efficacy analysis will be carried out using the patients from the FAS. Figures for selected efficacy endpoints, such as the primary pruritus endpoint, change in serum bile acids, and change in other patient-reported and caregiver-reported outcomes, will be provided by cohort/treatment subgroup and by visit. Forest plots will be provided for the efficacy subgroup analyses.

For efficacy endpoints derived from central laboratory data, if central laboratory data are not available due to COVID-19 or other reasons, local laboratory data will be used and converted to standard unit used by central laboratory. In addition, laboratory related efficacy endpoints will only be considered up to 14 days follow-up after the last dose.

9.6.1 Analysis Methods

Descriptive statistics mainly will be used in this open-label extension study unless otherwise specified.

9.6.2 Treatment by Centre Interaction Analysis (Multicentre Study)

NA

9.6.3 Analyses of Primary Efficacy Endpoints

All the primary analyses will be based on the FAS, unless otherwise specified.

For the EU and RoW, change from baseline 2 in fasting serum bile acids will be analysed by using the 1-sample t-test or the Wilcoxon signed rank test, as appropriate at the end of the 72-week treatment period based on the average of the values at Weeks 70 and 72. Baseline 2, defined in the table of derived variables in Appendix A, will be used to calculate change from baseline for the summary.

For Cohort 1 patients who were on odevixibat in Study A4250-005, change from Baseline 1 to end of the 72-week treatment in Study A4250-008 will be analysed by using the 1-sample t-test or the Wilcoxon signed rank test, as appropriate. Baseline 1,

defined in the table of derived variables in Appendix A, will be used for this statistical analysis.

For the US, the proportion of positive pruritus assessments at the patient level over the 72-week treatment period using the Albireo ObsRO instrument will be summarised descriptively. 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. At each assessment, the AM score will be compared to the baseline AM average, and the PM score will be compared to the baseline PM average. Both AM and PM pruritus assessments will be included in the analysis of this endpoint. For analysis purposes, diary entries will be assigned to a study day based on the recorded date regardless of recorded time. AM scores from the period of 14 days before or on the first dose day in Study A4250-008 will be averaged as AM baseline. PM scores from the period of 14 days before the first dose day in Study A4250-008 will be averaged as PM baseline. If a patient's baseline score is ≤1, then only the criterion of a one-point drop from baseline on the Albireo ObsRO instrument will be used to determine whether a pruritus assessment is positive or not for the primary endpoint analysis. Rounded baseline score will be used for the analysis.

A 95% CI will be provided for the proportion of positive pruritus assessments.

Change from Baseline 1 and 2 in monthly scratching severity score to end of the 72-week treatment in Study A4250-008 will be analysed by using the 1-sample t-test or the Wilcoxon signed rank test, as appropriate. Baseline 1 will only be used for patients in Cohort 1 who were on odevixibat in Study A4250-005.

9.6.4 Analyses of Secondary Endpoints

All secondary analyses will primarily be summarised descriptively based on the FAS, unless otherwise specified.

The change in secondary endpoints such as serum bile acids, growth, APRI score, Fib-4 score, PELD/MELD will be summarised by visit using descriptive statistics.

- Growth

Change in growth (height/length for age, weight for age, mid-arm circumference for age, and BMI for age) will be analysed by using the 1-sample t-test or the Wilcoxon signed

rank test, as appropriate at the end of the 72-week treatment period based on the average of the values at Weeks 70 and 72. In addition, change in growth will also be displayed using graphical presentations. Baseline 1 and 2, defined in the table of derived variables in Appendix A, will be used to calculate change from baseline for data analysis. Baseline 1 will only be used for patients in Cohort 1 who were on odevixibat in Study A4250-005.

The analysis of growth data for height/length, weight, and BMI will be based on calculated values using the software or methods from the Centers for Disease Control and Prevention (CDC) website for patients with age ≥2 years old and from the WHO website for patients with age <2 years old[7,8]. The analysis of growth data for mid-arm circumference will be based on calculated values for 2 months to 18 years for U.S. Children[9]. CRF collected growth data will be listed.

❖ Serum Bile Acids

For serum bile acids assessments, if a patient has assessments at Weeks 70 and 72, then the average of the 2 assessment values at Weeks 70 and 72 will be used for data analysis. This handling will also be applied to Weeks 22 and 24, and Weeks 46 and 48.

❖ Proportion of Positive Pruritus

The proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level on the Albireo ObsRO instrument from Weeks 0-4, Weeks 0-12, Weeks 0-22, Weeks 0-24, Weeks 0-36, Weeks 0-46, Weeks 0-48, Weeks 0-60, Weeks 0-70, or the proportion of positive pruritus assessments at each 4-week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between Visit 5/Week 24 to Visit 12/Week 76 will be summarised descriptively as for the primary analysis for the US. Similar summaries will be provided based on AM scores as well as PM scores.

[7] https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm following CDC's method

[8] https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas-who.htm following WHO's method

[9] Abdel-Rahman, Susan M et al. "Construction of Lambda, Mu, Sigma Values for Determining Mid-Upper Arm Circumference z Scores in U.S. Children Aged 2 Months Through 18 Years." Nutrition in clinical practice : official publication of the American Society for Parenteral and Enteral Nutrition vol. 32,1 (2017): 68-76.

The number and percent of patients achieving positive pruritus assessment for more than 50% of the time will be summarised by treatment group. Both AM and PM pruritus assessments will be included in the analysis of this endpoint. A cumulative distribution function (CDF) plot showing proportions of patients achieving positive pruritus assessment for more than X% of the time, X is the time of achieving positive pruritus assessment from 0 to 100%, by treatment group will be provided.

- Proportion of Responders for Pruritus Scores

The proportion of responders for pruritus scores will be tabulated by visit based on monthly scores and bi-weekly scores. The 95% CI of the proportion of responders will be provided, based on the exact method of Clopper-Pearson. A responder is defined as a patient who reports a decrease in pruritus score from unrounded baseline equivalent to or greater than the threshold of meaningful change estimated from the blinded psychometric analysis; the results of the blinded psychometric analysis across all anchors support a threshold of 1.0 point for AM, PM and AM and PM scratching scores. Baseline 1 and 2, defined in the table of derived variables in Appendix A, will be used for data analysis. Baseline 1 will only be used for patients in Cohort 1 who were on odevixibat in Study A4250-005.

- Biliary Diversion Surgery and Liver Transplantation

Number and percent of patients undergoing biliary diversion surgery and/or liver transplantation will be summarised by using descriptive statistics. A 95% CI also will be presented for the corresponding percentage. These parameters will be evaluated separately and together at Weeks 24, 48, 72 and all visits (every 16 weeks) during the optional extension period.

Kaplan-Meier curves will be used when appropriate for time-to-event data (that is, time to biliary diversion surgery or liver transplantation or death and time to any event). If a patient does not have any event, the patient will be censored at the last contact date. Median event-free times and associated 95% CIs will be calculated using Brookmeyer and Crowley methodology and a log-log transformation for constructing CIs.

- Fibroscan®

The change in APRI and Fib-4 score will be summarised using descriptive statistics from baseline 2 to Week 72 and all visits (every 16 weeks) during the optional extension period.

- PELD and MELD Score

The change in PELD and MELD will be summarised separately using descriptive statistics from baseline 2 to Week 72 and all visits (every 16 weeks) during the optional extension period.

- UDCA and/or Rifampicin

Percentages of patients in use of UDCA and/or Rifampicin at weeks 24, 48, and 72 will be presented in 4 categories, use of UDCA, use of Rifampicin, use of UDCA or Rifampicin, use of UDCA and Rifampicin. Percentage will be based on patients in study at week 24, 48, and 72.

Shift tables from Baseline 2 in use of UDCA and/or Rifampicin at Weeks 24, 48, and 72 will be presented in the following categories. “None”, “UCDA alone”, “Rifampicin alone”, “UCDA and Rifampicin”, “Early Termination”. Percentage will be based on patients in study at week 24, 48, and 72.

9.6.5 Analyses of Exploratory Endpoints

The exploratory efficacy variables are listed in Section 4.3. All exploratory analyses mainly will be summarised descriptively based on the FAS, unless otherwise specified.

Exploratory variables including ALT; GGT; total bilirubin; INR; albumin; liver enzymes; leukocytes and platelets; measures of bile acid synthesis; Albireo PRO and ObsRO itching/scratching severity scores; Albireo PRO and ObsRO sleep parameters; Global Symptom Relief; and PedsQL will be summarised descriptively. For continuous data, the change from baseline will be analysed in addition to the presentation of actual visit values. For categorical data, shift tables or frequency and percentages of patients will be presented, as appropriate. A line graph of itching/scratching daily severity scores of Albireo PRO and ObsRO over time will be provided for each patient.

For continuous data, such as ALT; GGT; total bilirubin; INR; albumin; liver enzymes; leukocytes and platelets; measures of bile acid synthesis; and the total score and domain score of PedsQL, the change from baseline 2 will be analysed descriptively in addition to the actual visit values. Global Symptom Relief at Weeks 4, 12, 24, 48, 72 and all visits (every 16 weeks) during the optional extension period will be summarised as categorical variables. Time points (visit windows) are specified in Appendix B.

- Proportion of Positive Pruritus

The proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level on the Albireo PRO instrument completed by patients ≥8 years of age only will also be explored and summarised in a similar fashion as for the secondary endpoint, the proportion of individual assessments meeting the definition of a positive pruritus assessment at the patient level on the Albireo ObsRO instrument.

Change from baseline 2 in PRO/ObsRO itching and scratching severity scores will be summarised by each 4-week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between Visit 5/Week 24 and Visit 12/Week 76. A summary table will be provided for night-time scores and morning time scores separately.

The pooled pruritus score including observer-reported scratching for patients <8 years of age and patient-reported itch severity for patients ≥8 years of age will be summarised in a similar manner.

The change from baseline 2 in PRO/ObsRO sleep parameters will be summarised at Week 72 as well as by each 4-week interval between Visit 1/Screening and Visit 5/Week 24, then by each visit between Visit 5/Week 24 and Visit 12/Week 76. Sleep parameters include difficulty of falling asleep and staying asleep, tiredness, and the number of awakenings.

- Fibroscan®

Change from baseline 2 in stage of liver fibrosis measured by Fibroscan® will be analysed descriptively. The frequencies of stages will be summarised by shift tables. Steatosis grade analysis will be performed in a similar fashion. Liver fibrosis as assessed by post-treatment biopsy will be listed and change from baseline may be presented, if available.

❖ Episodic Flares

Due to limited data availability and only 4 BRIC patients were enrolled in the study, the episodic flares data during the study will be presented as a listing.

9.7 Safety Analyses

All definitions relative to safety endpoints are detailed in Section 4.4.

All the safety analyses will be performed on the FAS for all safety variables specified below and summarised by cohort/treatment subgroup and overall.

For each safety variable, the last value collected before the first dose of study drug will be used as baseline (i.e., Baseline 2 defined in the table of derived variables in Appendix A) for all analyses unless otherwise specified.

In addition, different with efficacy analysis, laboratory related safety endpoints will be considered up to 28 days follow-up after the last dose.

9.7.1 Adverse Events

All AEs will be classified by Primary SOC and PT according to MedDRA, Version 26.0 or higher.

AEs will be classified as TEAEs and defined as follows:

A TEAE is an AE occurring during the treatment period and within 28 days follow-up after the last dose that a) Has a start date on or after the first dose date of study drug, or b) Has a start date before the date of the first dose date of study drug, but worsened in severity on or after the date of the first dose date of study drug. If an AE started in Study A4250-005 and was ongoing at the time of enrolment in Study A4250-008, the AE will not be considered a TEAE unless it worsens in severity on or after the date of the first dose date of study drug.

AEs with missing start dates, but with stop dates that either overlap with the treatment period or are missing, will be considered TEAEs. A TEAE with missing drug relationship- will be considered as related. A TEAE with missing severity will be

considered as severe. Details for imputing missing or partial start dates of AEs are described in Appendix D.

For counting of the number of AEs, if 2 AE records have the same preferred term and the start date of the 2nd AE is the same as or next day after the end date of the 1st AE, then they will be counted as one AE only.

An overall summary of the incidence of TEAEs (number of patients with any events and number of events, if applicable) will include the following:

- All TEAEs
- Drug-related TEAEs (AE will be defined as drug-related if causality is either probably, possibly, or definitely related)
- Severe TEAEs
- TEAEs leading to study discontinuation
- Serious TEAEs
- Drug-related serious TEAEs
- TEAEs leading to death
- Any hepatic TEAEs
    a. Any liver-related TEAE (events that, per the Investigator, are considered related to PFIC)
    b. Any suspected drug-induced liver injury (DILI) TEAEs (as adjudicated by the Data Safety Monitoring Board [DSMB] and defined in Section 9.7.1.2)
    c. Any TEAE of liver decompensation (as defined in Section 9.7.1.2)
    d. Drug related hepatic disorders – comprehensive search SMQ (narrow and broad)
- Any Fat-Soluble Vitamin Deficiency TEAEs refractory to clinically recommended vitamin supplementation (as defined in Section 9.7.1.1)
- Any Possible Sequelae of FSV Deficiency TEAEs by SOC and PT (Specified TEAEs with PTs are listed in Appendix G)

- Any Clinically Significant Diarrhoea TEAEs (as defined in Section 9.7.1.1)

TEAEs (number of patients with any events and number of events, if applicable) by SOC and PT in each treatment group will be tabulated for the following:

- TEAEs by SOC and PT including fat-soluble vitamin deficiencies, diarrhoea, hepatoxicity (as defined in Section 9.7.1.1). Note that hepatotoxicity will also be included with the tabulation of hepatic events
- All TEAEs by preferred term by descending incidence in Overall column
- TEAEs leading to study discontinuation by SOC and PT
- Serious TEAE by SOC and PT
- Drug-related serious TEAE by SOC and PT
- TEAEs leading to death by SOC and PT
- Common TEAEs (≥10% in overall)
- Hepatic TEAEs
    a. Liver-related TEAEs (events that, per the Investigator, are considered related to PFIC) by SOC and preferred term
    b. Suspected DILI events (as adjudicated by the DSMB and defined in Section 9.7.1.2)
    c. TEAEs of liver decompensation (as defined in Section 9.7.1.2) by SOC and preferred term
    d. Drug related hepatic disorders – comprehensive search SMQ (narrow and broad)

Summary tables for the number of patients with any TEAEs by SOC and PT by severity (mild, moderate, severe) and by causality (related [possibly, probably and definitely] versus unrelated [unlikely and unrelated]), will also be provided during the treatment period. AEs with the worst severity will be used in the by-severity summaries. Similarly, AEs with the worst causality (related to treatment) will be used in the by-causality summaries. If severity or causality is missing, data will be imputed to the worst category.

Where a patient has the same AE, based on PT, reported multiple times in the treatment period, the patient will only be counted once at the PT level in AE frequency tables. Where a patient has multiple AEs within the same SOC in the treatment period, the patient will only be counted once at the SOC level in AE frequency tables.

In the AE summaries, AEs will be sorted alphabetically by SOC and PT. In addition, the numbers of patients with liver-related mortality, liver-decompensation events, and all-cause mortality will be presented using descriptive statistics. Kaplan-Meier curves may be used for time-to-event data (time taken to experience liver-decompensation event, all-cause mortality, and biliary diversion surgery in weeks).

All AEs (including pre-treatment and post-treatment AEs), serious adverse events (SAEs), and deaths will be listed. Separate listings for AEs leading to dose interruption, AEs listing to dose change, and AEs of Interest (Fat-Soluble Vitamin Deficiency, Diarrhoea, Hepatic AEs, and Possible Sequelae of Fat-Soluble Vitamin Deficiency as defined below) will also be provided.

9.7.1.1 Definition for TEAEs of Fat-Soluble Vitamin Deficiency, Diarrhoea, and Hepatotoxicity

The following TEAEs have been defined based on the population under study:

- New or worsening of fat-soluble vitamin deficiency refractory to clinically recommended vitamin supplementation.

  All Investigator-reported verbatim terms related to decreases in vitamin levels or vitamin deficiency (e.g., preferred term of hypovitaminosis, Vitamin A decreased, Vitamin A deficiency) with the relevant concomitant medication records reviewed by the Medical Monitor, queried as needed, and the appropriate MedDRA preferred terms reported.

- Clinically significant diarrhoea, defined as any of the following:

  - Diarrhoea that persists for 21 or more days without any other aetiology based on medical review of other concurrent AEs for possible other causes of the diarrhoea or diagnostic testing (e.g., viral infections)

- Reported by the Investigator as severe in intensity or reported as an SAE due to the requirement for hospitalisation or as an important medical event
- Diarrhoea with concurrent dehydration requiring treatment with oral or intravenous rehydration and/or other treatment intervention based on medical review of AEs and concomitant medications

- Hepatoxicity: based on the SMQ of *Drug Related Hepatic Disorders*– comprehensive search SMQ (narrow and broad)
- Possible Sequelae of FSV Deficiency: based on the Specified TEAEs with PTs are listed in Appendix G.

For each of these categories, tabular summaries will be presented by MedDRA SOC and PT; the tables will also include the overall incidence of these AEs. Listings of patients with each of the events as defined will be provided.

9.7.1.2 Definitions and Determination of Hepatic Events

A DSMB was formed to independently assure the safety of patients enrolled in Study A4250-008, as well as to evaluate the integrity of study conduct and the data generated. The DSMB reviews the safety data at regular, pre-defined intervals and on an ad hoc basis as needed and makes recommendations regarding patient safety and study continuance (continuation, modification, or termination of the study). The DSMB is comprised of three paediatric hepatologists and an unblinded biostatistician.

As requested by the FDA, the DSMB has been chartered to review data from patients with hepatic AEs, including cases of suspected DILI and patients with liver decompensation events as defined below. The DSMB also reviews events that are reported in the SMQ of *Drug Related Hepatic Disorders; Severe Events Only*. The DSMB reviews each case and provides their expert opinion on the aetiology of the event.

For this review, Albireo prepares slides for presentation at the DSMB meeting on each patient who meets the criteria for hepatic event adjudication. Relevant liver-related laboratory values over time and a narrative summary of relevant information is provided to the DSMB. During the open session of the meeting, an Albireo physician reviews each case with the DSMB members, responds to questions, and/or obtains any additional

information requested by the DSMB. Albireo's assessment of the hepatotoxicity aetiology is documented for each event. During the closed session, the DSMB independently assesses the event aetiology which is documented on a Hepatic Event Adjudication Form that is attached to the meeting minutes. If the DSMB requests follow-up information, this is provided at the next scheduled meeting. The Adjudication Process Document outlines the events that will be adjudicated.

9.7.1.2.1 Suspected Drug-Induced Liver Injury

As outlined in the protocol for Study A4250-008, patients with laboratory criteria that meet any of the following are considered suspected events of DILI and undergo review and adjudication of the event aetiology by the DSMB:

- ALT or AST ≥5 × ULN if ALT or AST was normal at Baseline, or an absolute threshold of 800 U/L, whichever comes first
- ALT or AST ≥3 × Baseline if ALT or AST was abnormal at Baseline, or an absolute threshold of 800 U/L, whichever comes first
- ALT or AST ≥3 × Baseline or an absolute threshold increases of +300 U/L, whichever comes first, and total bilirubin >2 × ULN if total bilirubin was normal at Baseline
- ALT or AST >5 × ULN if they are normal at Baseline, or absolute threshold increases of +300 U/L if ALT or AST > ULN at Baseline in presence of normal LDH and CPK
- Doubling of total bilirubin if total bilirubin was <3 mg/dL at Baseline and total bilirubin is greater than 2 × ULN unrelated to hemolysis or established genetic diseases, such as Gilbert's Syndrome.
- Increase in total bilirubin by >3 mg/dL if total bilirubin was ≥3 mg/dL at Baseline
- INR increase to >1.5 if INR was normal at Baseline and increase is refractory to Vitamin K administration
- INR increase by >0.4 if INR was abnormal at Baseline and increase is refractory to Vitamin K administration

- Any increase in total bilirubin and transaminases if accompanied by either a symptom of clinical hepatitis (vomiting, nausea, right upper quadrant pain) or immunological reaction (rash or 5% eosinophilia)

9.7.1.2.2 Liver Decompensation Adverse Events

Events either identified by Investigators or meeting the Albireo definition of liver decompensation will undergo review and adjudication by the DSMB. Patients who meet either of the following criteria undergo review and adjudication of the event aetiology by the DSMB for liver decompensation:

- INR elevation >1.5 that is refractory to vitamin K administration
- In a patient with portal hypertension and cirrhosis, transition to decompensated cirrhosis evidenced by any of the following:
    - Presence of ascites
    - Hepatorenal syndrome
    - Portopulmonary hypertension
    - Hepatopulmonary syndrome
    - Variceal haemorrhage
    - Hepatic encephalopathy

9.7.1.2.3 SMQ Drug-Related Hepatic Disorder AEs:

Events in the Standardised MedDRA query SMQ *Drug Related Hepatic Disorders; Severe Events Only* (SMQ No. 20000007) that are not captured in any of the above parameters will be presented to the DSMB for review.

The data of all adjudicated hepatic events provided by the DSMB will also be listed.

9.7.2 Clinical Laboratory Evaluations

Clinical laboratory test results will be listed.

The following laboratory variables will be analyzed.

- Hematology:
  - Red blood cells and platelets: hemoglobin, hematocrit, red blood cell count, and platelet count
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, and eosinophils
- Clinical chemistry:
  - Metabolism: total cholesterol, triglycerides, creatine kinase, albumin
  - Electrolytes: sodium, potassium, chloride, calcium
  - Renal function: creatinine, blood urea nitrogen, estimated glomerular filtration rate
  - Liver function: ALT, AST, Alkaline phosphatase (and isoenzymes as applicable), direct bilirubin, total bilirubin, gamma-glutamyl transferase
  - Pregnancy test: Serum β-human chorionic gonadotropin (all female patients with positive urine pregnancy test)
- Urinalysis:
  - Urinalysis for quantitative analysis: pH, proteins, glucose, blood, ketones, leukocytes, and nitrites
- Other Labs: Vitamin A and E, 25-hydroxy vitamin D, INR, Alfa-fetoprotein (AFP), and Prothrombin Time

❖ Quantitative Analyses

For all laboratory variables above, descriptive statistics for clinical laboratory values (in SI units for all tests, and in conventional units for selected tests (Appendix F) and absolute changes from baseline at each post-baseline visit (Appendix B) will be presented. The change to the last visit will also be summarized. Central laboratory data will be used for the summary. If central laboratory data are not available due to COVID-19 or other reasons, local laboratory data will be used, if available.

Change from baseline in ALT, AST, GGT, direct bilirubin, total bilirubin will be summarized by visit using descriptive statistics. Figure of mean (± standard error [SE])

changes from baseline 2 will be provided at each available post-baseline visit. The figures will only present results in a treatment group if there's data for at least 5 patients at that visit; if all treatment groups at that visit do not have at least 5 patients' data, that visit will not be presented in the figure.

Evaluation of drug-induced serious hepatotoxicity (eDISH) plots will be presented for baseline and post-baseline liver function (ALT vs total bilirubin). Baseline eDISH plot will present concurrent levels of baseline ALT vs. total bilirubin as multiples of upper limit of normal (ULN). Post-baseline eDISH plot will present concurrent levels of peak ALT on treatment vs. peak total bilirubin within 30 days of peak ALT as multiples of ULN. In addition, a modified eDISH plot will present concurrent peak ALT vs peak total bilirubin as multiples of individual patient baseline values. Corresponding summary tables will be provided.

❖ Analyses according to reference normal range

Shift tables from baseline to the highest and lowest post-baseline value for quantitative variables will be presented for the clinical laboratory parameters. The laboratory results will be classified as low, normal, and high based on the normal range that was provided by central/local laboratories.
For ALT, AST and total bilirubin, a shift table based on the following classifications (per DILI guidance and CTCAE) will be presented:

- ALT and AST: ≤ 3 ULN, > 3 and ≤ 5 ULN, > 5 and ≤ 10 ULN, > 10 ULN
  Total Bilirubin: ≤ 2 ULN and > 2 ULN

❖ Liver Monitoring

Furthermore, a listing of patients meeting the following criteria for liver monitoring will be provided as follows:

- (ALT or AST ≥3× baseline or absolute threshold increase ≥ 300 U/L) and total bilirubin >2 ULN (normal baseline) at the same visit
- ALT or AST >5 ULN (normal baseline) or increase ≥ 300 U/L (baseline ALT or AST > ULN) in presence of normal LDH and CPK at the same visit

- INR increased to >1.5 (normal baseline) or increased by >0.4 relative to baseline (abnormal baseline)
- Total bilirubin ≥2× baseline (baseline total bilirubin <3 mg/dL) and total bilirubin is greater than 2× ULN, or increased by ≥3 mg/dL relative to baseline (baseline total bilirubin ≥3 mg/dL)

9.7.3 Vital Sign Measurements

Descriptive statistics for vital signs (temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, weight, height/length, mid-arm circumference, and BMI) and changes from baseline in vital signs at each post-baseline visit will be presented in a summary table. The change to the last visit will also be summarised. A shift table for the number of patients with changes from baseline to the highest or lowest value (Appendix E) will be provided by cohort/treatment subgroup during the treatment period.

Vital signs data will be listed.

9.7.4 Physical Examinations

All physical examination data (general appearance, eyes, ears, nose, throat, head/neck/thyroid, lymph nodes, cardiovascular, lungs/chest, abdomen, genitourinary, extremities, skin, musculoskeletal, neurological, and other body systems) will be summarised at each visit with percentages and frequencies along with abnormalities by cohort/treatment subgroup.

Abdominal ultrasound assessments for the liver, including Riedel's lobe, the portal vein, and the spleen also will be summarised descriptively for each visit.

Skin assessments on a 5-point scale (0-4 from no evidence of scratching to cutaneous bleeding, haemorrhage, scabbing) for face, right arm, left arm, right leg, left leg, and torso will be summarised at each visit with percentages and frequencies by cohort/treatment subgroup.

Physical examination and skin assessment data will be listed (including pre-treatment and post-treatment results).

9.8 Other Analyses

9.8.1 Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy endpoints for each of the following subgroups: age groups (<6 months, 6 months to 5 years, 6 to 12 years, and 13 to 18 years, >18 years), each PFIC type (1, 2, other, BRIC), region (US, EU, and RoW), sex, race, ethnicity, baseline serum bile acid (≥250 and <250 µmol/L), Child-Pugh classification, Bile Salt Export Pump (BSEP) type of PFIC 2 patients, and the use of UDCA, rifampicin (alone or either one). Subgroup analyses may be conducted for hepatic impairment classification per NCI Organ Dysfunction Working Group (ODWG) if appropriate.

9.8.2 Data Safety Monitoring Board

The DSMB will receive data in the form of tables, figures, and listings (provided by unblinded DSMB statistician from Firma who is independent to the Firma study team). The requirement for blinded or unblinded data is defined in the DSMB charter. Data provided to the DSMB will include, but is not limited to, demographics, baseline characteristics, medical and surgical history, prior and concomitant medications, AE and SAE data (by SOC and PT and by maximum intensity), laboratory data, liver monitoring, vital sign measurements, and abdominal ultrasound and patient disposition data.

10. Changes to Planned Analysis from Study Protocol

The changes to the planned analysis in the protocol are listed below.

1. Endpoints
    a. Removed below secondary efficacy endpoints
        i. All-cause mortality
        ii. Change in use of antipruritic medication at Weeks 24, 48, and 72
    b. Added below secondary efficacy endpoints
        i. Change in use of UDCA and/or Rifampicin at Weeks 24, 48, and 72
        ii. Proportion of responders for pruritus scores

c. Added below exploratory endpoint

   i. Change from baseline in episodic flares during the study treatment for BRIC patients.

d. Added below safety endpoint

   i. All-cause mortality

e. Updated secondary and exploratory efficacy endpoints to add the visits during extension period

2. Data Analysis

   a. For the number of patients with events (biliary diversion surgery or liver transplantation or death) and time to event, the comparison to the NAPPED population will be not included in this SAP and will be performed separately.

   b. The following analysis in the protocol "As an exploratory analysis of pruritus and serum bile acids, a comparison of treatment with A4250 120 µg/kg/day during the first 24 weeks of Study A4250-008 versus placebo patients over the 24week treatment period from Study A4250-005 will be carried out." was conducted in A4250 ISE analysis because Study A4250-008 did not have post-baseline data of Study A4250-005.

3. TEAE definition is updated from "during treatment period" to "during treatment period and within 28 days follow-up after the last dose".

4. Laboratory data will only be considered up to 14 days follow-up after the last dose of Odevixibat for efficacy related endpoints.

5. For any hepatic TEAEs, add "Drug related hepatic disorders – comprehensive search SMQ (narrow and broad)".

11. Appendices

Appendix A: Derived Variables

A list of derived variables for demographic and baseline characteristics, various duration derivations, drug compliance, baseline derivations, and other important derivations applicable for this study is presented in Table 3.

Table 3: Derived Variables for Demographic and Baseline Characteristics, Various Duration Derivations, Drug Compliance, Baseline Derivations, and Other Important Derivations

VARIABLES	FORMULA
Demographic and Baseline Characteristics	
Age at informed consent (in years)	Cohort 1: For patients not from France and Germany, age will be calculated based on date of birth. For patients from France and Germany, only birth year was collected, and July 1 was imputed in the eDC system. The CRF collected age months and age years are based on the imputed date of birth. For analysis purpose, age will be calculated based on collected age months and age years on the Study A4250-005 CRF or the external file (primary source). Cohort 2: For patients not from France and Germany, age will be calculated based on date of birth. For patients from France and Germany, only birth year was collected, and July 1 was imputed in the eDC system. The CRF collected age months and age years are based on the imputed date of birth. For analysis purpose, age will be calculated based on collected age months and age years on the Study A4250-008 CRF or the external file (primary source).
BMI (kg/m^2)	Weight (kg)/[height (m^2)
PFIC diagnosis (in years)	Will be derived by SAS YRDIF function YRDIF (date of diagnosis of PFIC, date of informed consent, 'ACT/ACT')
Derivation of Duration	
Study day at any visit	Date of interest–date of first dose of study drug. One day is added if this difference is ≥0
Extent of exposure (days)	Date of last study drug intake–date of first study drug intake + 1
Drug Compliance	
Compliance based on CRF data	100 × [(total number of capsules dispensed – total number of capsules returned) /(total number of capsules planned to be taken)]. This will be considered as the primary compliance rate.
Compliance based on eDiary data up to week 24	100 × (total number of capsules taken up to week 24/total number of capsules planned to be taken up to week 24).

VARIABLES	FORMULA
	The number of capsules planned to be taken will be estimated based on patient's body weight per Protocol Table 3. If a patient's weight changes at any time during the study, dose adjustment will be required.
Derivations for Efficacy Parameters	
Baseline (general)	Baseline 1 is defined as the last value prior to the first dose in Study A4250-005 for patients in Cohort 1. Baseline 2 is defined as the last value prior to the first dose in Study A4250-008 for all patients. For patients in Cohort 1, the pre-dose assessments of Study A4250-008 can be from Study A4250-005. Baseline 2 will be used in all analyses unless otherwise specified.
Baseline for serum bile acids change from baseline	Baseline 1 is defined for patients in Cohort 1 and will be calculated as the average of last 2 values prior to the first dose in Study A4250-005. If only one non-missing value is available, it will be used as baseline. Baseline 2 is defined as follows: Cohort 1: the average of the last 2 values before the first dose of study drug in Study A4250-008. In general, these 2 values are the values of the last 2 assessments of Study A4250-005. If pre-dose assessments are collected in Study A4250-008 for a patient, then the values of pre-dose assessments in Study A4250-008 will be considered first and used to calculate the baseline. These 2 values need to be taken from 2 consecutive scheduled visits or unscheduled visits. If only one value is available from 2 consecutive scheduled visits or unscheduled visits, then that value will be used as baseline. Cohort 2: the average of last 2 values prior to the first dose in Study A4250-008. If only one non-missing value is available, it will be used as baseline. Baseline 2 will be used in all analyses unless otherwise specified.
End value for serum bile acids change from baseline	The end value is the average of the values at Weeks 70 and 72 after the start of treatment. (Appendix B). If one value is missing, then the non-missing value will be used as the end value. If both values are missing, then the end value is missing.
Baseline, daily, weekly, and monthly score by AM and PM respectively (scratching, itch severity)	For both the Albireo ObsRO scratching item and the Albireo PRO itch severity score: All non-missing AM scores from the period of 14 days before or on the first dose day of study medications will be averaged as baseline. All non-missing PM scores from the period of 14 days before the first dose day of study medications will be averaged as baseline. Baseline score will be considered missing if ≥8 out of 14 assessments in the 14 days are missing (i.e. 50% rule is applied based on the number of planned assessments). A weekly AM (PM) score will be calculated by averaging all non-missing AM (PM) scores in a week. A weekly score will be considered missing if ≥4 out of 7 AM (PM) scores in a week are missing.

VARIABLES	FORMULA
	A monthly AM (PM) score will be calculated by averaging all non-missing AM (PM) scores in a month (28 days). A monthly score will be considered missing if ≥15 out of 28 AM (PM) scores a week are missing. An AM (PM) average score at each visit after Week 24 will be calculated by averaging all non-missing AM (PM) scores between 2 visits with analysis windows applied (Appendix B). 50% rule is applied based on the number of planned assessments.
AM & PM baseline, daily, weekly, and monthly score (scratching, itch severity)	For both the Albireo ObsRO scratching item and the Albireo PRO itch severity score: A daily AM & PM score will be averaged from the 2 ratings for each day. A daily score will be considered missing if both assessments are missing. A weekly score will be calculated by averaging all non-missing AM and PM scores in a week. A weekly score will be considered missing if ≥8 out of 14 assessments in a week are missing. A monthly score will be calculated by averaging all non-missing AM and PM scores in a month (28 days). A monthly score will be considered missing if ≥29 out of 56 assessments in a month are missing. An average score of AM & PM at each visit after Week 24 will be calculated by averaging all non-missing AM and PM scores between 2 visits with analysis windows applied (Appendix B). 50% rule is applied based on the number of planned assessments. All non-missing AM scores from the period of 14 days before or on the first dose day of study medications, and all non-missing PM scores from the period of 14 days before the first dose day of study medications will be averaged as the AM & PM baseline score. Baseline score will be considered missing if ≥15 out of 28 assessments in the 14 days are missing. Rounded baseline score will be used for the analysis. One thing of note: Inclusion criteria No. 4 in Study A4250-005: Cohort 1: Patient must have history of significant pruritus and a caregiver-reported observed scratching in the eDiary average of ≥2 (on 0 to 4 scale) in the 2 weeks prior to randomisation in Study A4250-005. Inclusion criteria No. 4 in Study A4250-008: Cohort 2: Patient must have history of significant pruritus and a caregiver-reported observed scratching or patient reported itching (for patients >18 with no caregiver-reported observed scratching) in the eDiary average of ≥2 (on 0 to 4 scale) in the 2 weeks prior to the screening/inclusion visit (Visit 1) in Study A4250-008. The pruritus score for purposes of establishing eligibility was calculated by taking the average of the worse of the two scores for each day. The values for week one were averaged and the values for week 2 were averaged. The two weekly averages were then averaged to provide a single score. If this score was ≥2 the pruritus eligibility requirement was met. The calculation of pruritus eligibility score is different from the calculation of the baseline pruritus score defined in the SAP.

VARIABLES	FORMULA
Average of change from baseline from each AM and PM scores (scratching, itch severity)	The calculation below is based on the change from baseline in each AM and PM score. The values based on this calculation will be used for data analysis. Change from baseline (daily) will be calculated by averaging all non-missing values of change from baseline (AM and PM) in a day. A daily change from baseline will be considered missing if both AM and PM change from baseline in a day are missing. Change from baseline (weekly) will be calculated by averaging all non-missing values of change from baseline (AM and PM) in a week. A weekly change from baseline will be considered missing if ≥8 out of 14 change from baseline values in a week are missing. Change from baseline (monthly) will be calculated by averaging all non-missing values of change from baseline (AM and PM) in a month (28 days). A monthly change from baseline will be considered missing if ≥29 out of 56 assessments in a month are missing. Change from baseline at each visit after Week 24 will be calculated by averaging all non-missing values of change from baseline (AM and PM) between 2 visits with analysis windows applied (Appendix B). 50% rule is applied based on the number of planned assessments.
Baseline, daily, weekly, and monthly (sleep parameters, such as difficulty falling asleep and staying asleep, tiredness, the number of awakenings)	For patient- and observer-reported outcome scores of sleep parameters, the same approach above will be used as for scratching/itch severity by AM and PM, respectively, since there is just one rating per day.
Proportion of positive pruritus assessments	No imputation will be made for any missing data. The assessments after intercurrent events (premature treatment discontinuation, death, or initiation of rescue treatments such as biliary diversion surgery or liver transplantation) will be treated as missing and excluded from analysis. The proportion of positive pruritus assessments will be calculated based on reported eDiary data only. 50% rule will be applied based on the number of planned assessments (Appendix B).

VARIABLES	FORMULA
Baseline for proportion of responders for pruritus scores	Baseline 1 is defined as the average of all non-missing daily scores from 14 days prior to the first dose of study drug in study A4250-005. Baseline 2 is defined as the average of all non-missing daily scores from 14 days prior to the first dose of study drug in study A4250-008 (For patients in Cohort 1, the pre-dose assessments of Study A4250-008 can be from Study A4250-005). Baseline score will be considered missing if ≥8 out of 14 assessments in the 14 days are missing. The unrounded baseline score will be used for the analysis.
Derivations for Safety Parameters	
AE duration (days)	AE end date–AE start date + 1
TEAEs	An AE (classified by preferred term) occurring during the treatment period and within 28 days follow-up after the last dose that a) has a start date on or after the first dose date of study drug, or b) has a start date before the date of the first dose date of study drug, but worsened in severity on or after the date of the first dose date of study drug. If an AE started in Study A4250-005 and was ongoing at the time of enrolment in Study A4250-008, the AE will not be considered a TEAE unless it worsens in severity on or after the date of the first dose date of study drug.

AE: adverse event; BMI: body mass index; CRF: case report form; eDiary: electronic diary; ObsRO: observer-reported outcome; PFIC: progressive familial intrahepatic cholestasis; PRO: patient-reported outcome; SAP: statistical analysis plan; TEAEs: treatment-emergent adverse events

Appendix B: Visit Window

The observation closest to the target day is the measurement used in the analysis for each visit. The following visit window will apply for all laboratory parameters, questionnaires, vital signs, physical measurements and other efficacy parameters in the study, if not otherwise specified.

Table 4: Analysis Visit Window (General)

TIMING OF ASSESSMENT (DAYS RELATIVE TO TREATMENT)	VISIT NAME TO DISPLAY FOR ANALYSIS	TARGET DAY	STUDY DAY (RELATIVE DAY)
Screening (Days -56 to -1)	Baseline		≤ -1
Day 1 Week 1	Baseline		1 (Pre-dose)
Week 4 (± 5 days)	Week 4	28	Post-baseline - 56
Week 12 (± 7 days)	Week 12	84	57–119
Week 22 (± 7 days)	Week 22	154	120–161
Week 24 (± 7 days)	Week 24	168	162–210
Week 36 (± 7 days)	Week 36	252	211–287
Week 46 (± 7 days)	Week 46	322	288–329
Week 48 (± 7 days)	Week 48	336	330–378
Week 60 (± 7 days)	Week 60	420	379–455
Week 70 (± 7 days)	Week 70	490	456–497
Week 72/EOT (± 7 days)	Week 72	504	498–(Last dose day + 14)
4 weeks post last dose of study drug (±7 days)	Follow-up	28 post last dose	Last dose day + 15– Last dose day + 28
For patients who enter optional extension period:			
Week 72/EOT (± 7 days)	Week 72	504	498– Min(518, start day of optional extension period -1)
Week 88	Week 88	616	Min(519, start day of optional extension period)–672
Week 104, 120, … (continue every 16 weeks)	Week 104, 120, … (continue every 16 weeks)	7*week #	(7*(week # - 8) + 1) – Min(7*(week # + 8), Last dose day + 14)

Table 5: Analysis Visit Windows for GIC/GIS, Physical Measurements and Selected Lab Test)

TIMING OF ASSESSMENT (DAYS RELATIVE TO TREATMENT)	VISIT NAME TO DISPLAY FOR ANALYSIS	TARGET DAY	STUDY DAY (RELATIVE DAY)
Screening (Days -56 to -1)	Baseline		≤ -1
Day 1 Week 1	Baseline		1 (Pre-dose)
Week 4 (± 5 days)	Week 4	28	Post-baseline - 56
Week 12 (± 7 days)	Week 12	84	57–126
Week 24 (± 7 days)	Week 24	168	127–252
Week 48 (± 7 days)	Week 48	336	253–420
Week 72/EOT (± 7 days)	Week 72	504	421–(Last dose day + 14)
4 weeks post last dose of study drug (±7 days)	Follow-up	28 post last dose	Last dose day + 15– Last dose day + 28
For patients who enter optional extension period:			
Week 72/EOT (± 7 days)	Week 72	504	421– Min(518, start day of optional extension period -1)
Week 88	Week 88	616	Min(519, start day of optional extension period)–672
Week 104, 120, … (continue every 16 weeks)	Week 104, 120, … (continue every 16 weeks)	7*week #	(7*(week # - 8) + 1) – Min(7*(week # + 8), Last dose day + 14)

Note: Physical measurements include physical examination, voluntary photography and skin examination. Selected lab tests include urinalysis and autotaxin, p-C4.

Table 6: Analysis Visit Window for PedsQL, Fibroscan, Abdominal Ultrasound and AFP

TIMING OF ASSESSMENT (DAYS RELATIVE TO TREATMENT)	VISIT NAME TO DISPLAY FOR ANALYSIS	TARGET DAY	STUDY DAY (RELATIVE DAY)
Screening (Days -56 to -1)	Baseline		≤ -1
Day 1 Week 1	Baseline		1 (Pre-dose)
Week 24 (± 7 days)	Week 24	168	71 –252
Week 48 (± 7 days)	Week 48	336	253–420
Week 72/EOT (± 7 days)	Week 72	504	421–(last dose day + 14)
4 weeks post last dose of study drug (±7 days)	Follow-up	28 post last dose	Last dose day + 15– Last dose day + 28
For patients who enter optional extension period:			
Week 72/EOT (± 7 days)	Week 72	504	421– Min(518, start day of optional extension period -1)
Week 88	Week 88	616	Min(519, start day of optional extension period)–672
Week 104, 120, … (continue every 16 weeks)	Week 104, 120, … (continue every 16 weeks)	7*week #	(7*(week # - 8) + 1) – Min(7*(week # + 8), Last dose day + 14)

For laboratory and non-laboratory parameters, if a patient has more than one measurement included within a window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day, the earlier assessment will be used. For laboratory parameters, central laboratory results will be used over local laboratory results if both are in a same analysis window.

Derivations for pruritus and other itching, scratching, sleep parameters measured by Albireo ObsRO and PRO instruments will be derived based on the following analysis window. For analysis purposes, diary entries will be assigned to a study day based on the recorded date regardless of recorded time. Please refer to the derivations in the table of derived variables in Appendix A for details.

Table 7: Analysis Visit Window for eDiary Parameters

4-WEEK/BY-VISIT INTERVAL	INTERVALS TO INCLUDE EDIARY DATA (DAYS)[a]	INTERVALS WITH >=50% OF EXPECTED DATA TO INCLUDE PATIENTS[b] (# OF EXPECTED DAYS TO REPORT EDIARY)
Weeks 1 – 4	1 - 28	Weeks 1 – 4 (28 days)
Weeks 5 – 8	29 – 56	Weeks 5 – 8 (28 days)
Weeks 9 – 12	57 – 84	Weeks 9 – 12 (28 days)
Weeks 13 – 16	85 – 112	Weeks 13 – 16 (28 days)
Weeks 17 – 20	113 – 140	Weeks 17 – 20 (28 days)
Weeks 21 – 24	141 – 168	Weeks 21 – 24 (28 days)
Weeks 34 – 36	169 – 287	Weeks 31 – 41 (21 days)
Weeks 44 – 46	288 – 322	Weeks 42 – 46 (21 days)
Weeks 47 – 48	323 – 378	Weeks 47 – 54 (14 days)
Weeks 58 – 60	379 – 455	Weeks 55 – 65 (21 days)
Weeks 68 – 70	456 – 490	Weeks 66 – 70 (21 days)
Weeks 71 – 72	491 – 504	Weeks 71 – 72 (14 days)
Weeks 72 – 76	>=505	>=505 (28 days)

[a] The proportion of positive pruritus assessments is calculated based on reported data only. The assessments after intercurrent events (premature treatment discontinuation, death, or initiation of rescue treatments such as biliary diversion surgery or liver transplantation) will be excluded from the calculation.
[b] To have an appropriate analysis, only include patients who reported at least 50% of expected data during the interval. Of notes, for Weeks 34 – 36, while eDiary data during weeks 25 to 41 will be included for analysis, 50% rule is applied to Weeks 31 – 41 only to make sure that a patient is on treatment long enough for the analysis of Weeks 34 – 36.

Table 8: Analysis Visit Window for Proportion of Responders for Pruritus Monthly Scores

4-WEEK/BY-VISIT INTERVAL	INTERVALS TO INCLUDE EDIARY DATA (DAYS)[a]	INTERVALS WITH >=50% OF EXPECTED DATA TO INCLUDE PATIENTS[b] (# OF EXPECTED DAYS TO REPORT EDIARY)
Weeks 1 – 4	1 - 28	Weeks 1 – 4 (28 days)
Weeks 5 – 8	29 – 56	Weeks 5 – 8 (28 days)
Weeks 9 – 12	57 – 84	Weeks 9 – 12 (28 days)
Weeks 13 – 16	85 – 112	Weeks 13 – 16 (28 days)
Weeks 17 – 20	113 – 140	Weeks 17 – 20 (28 days)
Weeks 21 – 24	141 – 168	Weeks 21 – 24 (28 days)
Weeks 34 – 36	169 – 287	Weeks 31 – 41 (21 days)
Weeks 45 – 48	288 – 378	Weeks 42 – 54 (28 days)
Weeks 58 – 60	379 – 455	Weeks 55 – 65 (21 days)
Weeks 68 – 72	456 – 504	Weeks 66 – 72 (28 days)

[a] The proportion of responders for pruritus monthly scores is calculated based on reported data only. The assessments after intercurrent events (premature treatment discontinuation, death, or initiation of rescue treatments such as biliary diversion surgery or liver transplantation) will be excluded from the calculation.
[b] To have an appropriate analysis, only include patients who reported at least 50% of expected data during the interval. Of notes, for Weeks 34 – 36, while eDiary data during weeks 25 to 41 will be included for analysis, 50% rule is applied to Weeks 31 – 41 only to make sure that a patient is on treatment long enough for the analysis of Weeks 34 – 36.

Table 9: Analysis Visit Window for Proportion of Responders for Pruritus Bi-weekly Scores

BI-WEEKLY/BY-VISIT INTERVAL	INTERVALS TO INCLUDE EDIARY DATA (DAYS)[a]	INTERVALS WITH >=50% OF EXPECTED DATA TO INCLUDE PATIENTS[b] (# OF EXPECTED DAYS TO REPORT EDIARY)
Weeks 1 – 2	1 - 14	Weeks 1 – 2 (14 days)
Weeks 3 – 4	15 - 28	Weeks 3 – 4 (14 days)
Weeks 5 – 6	29 – 42	Weeks 5 – 6 (14 days)
Weeks 7 – 8	43 – 56	Weeks 7 – 8 (14 days)
Weeks 9 – 10	57 – 70	Weeks 9 – 10 (14 days)
Weeks 11 – 12	71 – 84	Weeks 11 – 12 (14 days)
Weeks 13 – 14	85 – 98	Weeks 13 – 14 (14 days)
Weeks 15 – 16	99 – 112	Weeks 15 – 16 (14 days)
Weeks 17 – 18	113 – 126	Weeks 17 – 18 (14 days)
Weeks 19 – 20	127 – 140	Weeks 19 – 20 (14 days)
Weeks 21 – 22	141 – 154	Weeks 21 – 22 (14 days)
Weeks 23 – 24	155 – 168	Weeks 23 – 24 (14 days)
Weeks 35 – 36	239 – 252	Weeks 35 – 36 (14 days)
Weeks 47 – 48	323 – 336	Weeks 47 – 48 (14 days)
Weeks 59 – 60	407 – 420	Weeks 59 – 60 (14 days)
Weeks 71 – 72	491 – 504	Weeks 71 – 72 (14 days)

[a] The proportion of responders for pruritus bi-weekly scores is calculated based on reported data only. The assessments after intercurrent events (premature treatment discontinuation, death, or initiation of rescue treatments such as biliary diversion surgery or liver transplantation) will be excluded from the calculation.
[b] To have an appropriate analysis, only include patients who reported at least 50% of expected data during the interval. Of notes, for Weeks 35 – 36, while eDiary data during weeks 35 to 36 will be included for analysis, 50% rule is applied to Weeks 35 – 46 only to make sure that a patient is on treatment long enough for the analysis of Weeks 35 – 36.

Table 10: Analysis Visit Window for Proportion of Positive Pruritus Assessment

CUMULATIVE INTERVAL	INTERVALS TO INCLUDE EDIARY DATA (DAYS)[a] (# OF EXPECTED DAYS TO REPORT EDIARY)	INTERVALS WITH >=50% OF EXPECTED DATA TO INCLUDE PATIENTS[b] (# OF EXPECTED DAYS TO REPORT EDIARY)
Weeks 0 – 4	1 – 28 (28 days)	Weeks 1 – 4 (28 days)
Weeks 0 – 12	1 – 84 (84 days)	Weeks 9 – 12 (28 days)
Weeks 0 – 22	1 – 154 (154 days)	Weeks 19 – 22 (28 days)
Weeks 0 – 24	1 – 168 (168 days)	Weeks 21 – 24 (28 days)
Weeks 0 – 36	1 – 287 (189 days)	Weeks 31 – 41 (21 days)
Weeks 0 – 46	1 – 322 (210 days)	Weeks 42 – 46 (21 days)
Weeks 0 – 48	1 – 378 (224 days)	Weeks 47 – 54 (14 days)
Weeks 0 – 60	1 – 455 (245 days)	Weeks 55 – 65 (21 days)
Weeks 0 – 70	1 – 490 (266 days)	Weeks 66 – 70 (21 days)
Weeks 0 – 72	1 – 504 (280 days)	Weeks 71 – 72 (14 days)

[a] The proportion of positive pruritus assessments is calculated based on reported data only when >=50% of expected ediary data is reported. The assessments after intercurrent events (premature treatment discontinuation, death, or initiation of rescue treatments such as biliary diversion surgery or liver transplantation) will be excluded from the calculation.
[b] To have an appropriate analysis, only include patients who reported at least 50% of expected data during the interval. Of notes, for Weeks 0 – 36, while eDiary data during weeks 0 to 41 will be included for analysis, 50% rule is applied to Weeks 31 – 41 only to make sure than a patient is on treatment long enough for the analysis of Weeks 0 – 36.

Appendix C: Definition of Region Variable

The list of country, country code, and region variable are provided in Table 11.

Table 11: Definition of Region Variable

COUNTRY	COUNTRY CODE	REGION VARIABLE
Australia	AUS	RoW
Belgium	BEL	EU
Canada	CAN	RoW
France	FRA	EU
Germany	DEU	EU
Israel	ISR	RoW
Italy	ITA	EU
Netherlands	NLD	EU
Poland	POL	EU
Saudi Arabia	SAU	RoW
Spain	ESP	EU
Sweden	SWE	EU
Turkey	TUR	RoW
United Kingdom	GBR	EU
United States	USA	US

EU: European Union; RoW: rest of world; US: United States

Appendix D: Handling of Missing or Incomplete Dates

Global Statement:

If the imputed date is prior to the date of birth, then impute the missing date as date of birth.

Imputation rules for missing or partial AE start date are defined below:

If only Day of AE start date is missing:

If the AE start year and month are the same as that for the first dose date, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start day as the day of first dose date

- If AE end date is prior to first dose date, then impute the AE start day as 1

If Day and Month of AE start date are missing:

If AE start year = first dose year, then:

- If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then impute the AE start month and day as the month and day of first dose date
- If AE end date is prior to first dose date, then impute the AE start month as January and the day as 1

If Year of AE start date is missing:

If the year of AE start is missing or AE start date is completely missing, then query the site with no imputation. Also compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date, then the AE should be considered as a pre-treatment AE. Otherwise, the AE will be considered as TEAE.

Imputation rules for missing or partial non-study medication start/stop dates are defined below:

Missing or partial non-study medication start date:

- If only day is missing, use the first day of the month
- If day and month are both missing, use the first day of the year
- If day, month, and year are all missing, use the date of the day before the first dose date

Missing or partial non-study medication stop date:

- If only day is missing, use the last day of the month
- If day and month are both missing, use the last day of the year
- If day, month, and year are all missing, assign “continuing” status to stop date

Appendix E: Normal Reference Ranges of Vital Signs[10]

Table 12: Heart Rate by Age (Beats/Minute) Reference

AGE	AWAKE RATE
Infant (<1 year)	100-190
Toddler (1-2 years)	98-140
Preschool (3-5 years)	80-120
School-age (6-11 years)	75-118
Adolescent (12-15 years)	60-100
> 15 years	60-100

Table 13: Normal Respiratory Rate by Age (Breaths/Minute) Reference

AGE	RESPIRATORY RATE
Infants (<1 year)	30-53
Toddler (1-2 years)	22-37
Preschool (3-5 years)	20-28
School-age (6-11 years)	18-25
Adolescent (12-15 years)	12-20
>15 years	12-20

Table 14: Normal Blood Pressure by Age (mm Hg) Reference

AGE	SYSTOLIC PRESSURE	DIASTOLIC PRESSURE
Infant (<1 year)	72-104	37-56
Toddler (1-2 years)	86-106	42-63
Preschooler (3-5 years)	89-112	46-72
School-age (6-9 years)	97-115	57-76
Preadolescent (10-11 years)	102-120	61-80
Adolescent (12-15 years)	110-131	64-83
>15 years	90-120	50-80

[10] Pediatric Vital Signs Reference Chart. Peds cases - Pediatrics for Medical Students - Developed by Chris Novak and Peter Gill for PedsCases.com April 21, 2016 (http://www.pedscases.com/pediatric-vital-signsreference-Chart).

Table 15: Normal Temperature Range by Method

METHOD	TEMPERATURE (°C)
Rectal	36.6-38
Ear	35.8-38
Oral	35.5-37.5
Axillary	36.5-37.5
Temporal/core[a]	35.8-38

[a] In the eCRF core and temporal temperature measurements can be ticked as methods. Rectal and Tympanic (ear) fall in this group. Additionally, temporal temperature measurements (using a temperature scanner on the forehead)–approximate closely to core temperature measurements and therefore can be classified in this category. For that reason, the normal temperature range for core and temporal temperature measurements will be defined as described.

Appendix F: SI and US Conventional Units of Clinical Laboratory Values

SERUM CHEMISTRY	SI UNIT	CONVENTIONAL UNIT
Analyte		
Alpha Fetoprotein	IU/mL	ng/mL
Direct bilirubin	µmol/L	mg/dL
Calcium	mmol/L	mg/dL
Chloride	mmol/L	mEq/L
Creatinine	µmol/L	mg/dL
Potassium	mmol/L	mEq/L
Sodium	mmol/L	mEq/L
Serum bile acid	µmol/L	µg/mL
Total bilirubin	µmol/L	mg/dL
Haematology	**SI Unit**	**Conventional Unit**
Analyte		
Haematocrit	ratio (L/L)	%
Haemoglobin	g/L	g/dL
Red blood count (RBC)	x10^12/L	x10^6/µL
Platelet count	x10^9/L	x10^3/µL
White blood cell count	x10^9/L	x10^3/µL
Fat Soluble Vitamins	**SI Unit**	**Conventional Unit**
Vitamin A	µmol/L	ug/dL
Vitamin E	µmol/L	mg/L
Vitamin D (25-dihydroxy)	nmol/L	ng/mL
Vitamin K	nmol/L	ng/mL
Urinalysis	**SI Unit**	**Conventional Unit**
Analyte		
Glucose	mmol/L	mg/dL
Ketones	mmol/L	mg/dL
Protein	mmol/L	mg/dL

Appendix G: PT Term of Possible Sequelae of FSV Deficiency

PT Term	Code
Acetabulum fracture	10000397
Activated partial thromboplastin time abnormal	10000631
Activated partial thromboplastin time prolonged	10000636
Adrenal haemorrhage	10001361
Alopecia	10001760
Anastomotic ulcer haemorrhage	10002244
Ankle fracture	10002544
Aortic aneurysm rupture	10002886
Areflexia	10003084
Arrhythmia	10003119
Arterial rupture	10003173
Auricular haematoma	10003797
Bleeding varicose vein	10005144
Blindness	10005169
Blindness transient	10005184
Blood blister	10005372
Blood calcium decreased	10005395
Blood urine	10005863
Bone pain	10006002
Brain stem haemorrhage	10006145
Breast haemorrhage	10006254
Broad ligament haematoma	10006375
Calcium deficiency	10006956
Cephalhaematoma	10008014
Cerebellar haemorrhage	10008030
Cerebral aneurysm ruptured syphilitic	10008076
Cerebral arteriovenous malformation haemorrhagic	10008086
Cerebral haemorrhage	10008111
Cerebral haemorrhage neonatal	10008112
Choroidal haemorrhage	10008786
Clavicle fracture	10009245
Closed fracture manipulation	10009506
Coagulation factor IX level decreased	10009746
Coagulation factor VII level decreased	10009761
Coagulation factor X level decreased	10009775
Coagulation time prolonged	10009799

PT Term	Code
Coagulopathy	10009802
Colonic haematoma	10009996
Complicated fracture	10010149
Compression fracture	10010214
Congenital anomaly	10010356
Conjunctival haemorrhage	10010719
Corneal scar	10011044
Cystitis haemorrhagic	10011793
Decreased immune responsiveness	10011968
Dementia	10012267
Dental caries	10012318
Diarrhoea haemorrhagic	10012741
Disseminated intravascular coagulation	10013442
Diverticulitis intestinal haemorrhagic	10013541
Diverticulum intestinal haemorrhagic	10013560
Dry eye	10013774
Duodenal ulcer haemorrhage	10013839
Duodenitis haemorrhagic	10013865
Dwarfism	10013883
Dysarthria	10013887
Dysphagia	10013950
Ear haemorrhage	10014009
Ecchymosis	10014080
Encephalitis haemorrhagic	10014589
Enterocolitis haemorrhagic	10014896
Epistaxis	10015090
Exsanguination	10015719
External fixation of fracture	10015741
Extradural haematoma	10015769
Extravasation blood	10015867
Eye haemorrhage	10015926
Factor IX deficiency	10016077
Femoral neck fracture	10016450
Femur fracture	10016454
Fibula fracture	10016667
Foetal-maternal haemorrhage	10016871
Foot fracture	10016970
Forearm fracture	10016997

PT Term	Code
Fracture	10017076
Fracture delayed union	10017081
Fracture malunion	10017085
Fracture nonunion	10017088
Fractured sacrum	10017308
Gait disturbance	10017577
Gastric haemorrhage	10017788
Gastric ulcer haemorrhage	10017826
Gastric ulcer haemorrhage, obstructive	10017829
Gastritis alcoholic haemorrhagic	10017857
Gastritis haemorrhagic	10017866
Gastrointestinal haemorrhage	10017955
Gingival bleeding	10018276
Greenstick fracture	10018720
Haemarthrosis	10018829
Haematemesis	10018830
Haematocoele	10018833
Haematochezia	10018836
Haematoma	10018852
Haematospermia	10018866
Haematuria	10018867
Blood urine present	10018870
Haematuria traumatic	10018871
Haemoperitoneum	10018935
Haemoptysis	10018964
Haemorrhage in pregnancy	10018981
Haemorrhage intracranial	10018985
Haemorrhage subcutaneous	10018999
Haemorrhage subepidermal	10019001
Haemorrhagic cerebral infarction	10019005
Haemorrhagic disease of newborn	10019008
Haemorrhagic disorder	10019009
Haemorrhagic infarction	10019013
Haemorrhagic stroke	10019016
Haemothorax	10019027
Hand fracture	10019114
Henoch-Schonlein purpura	10019617
Hepatic haematoma	10019676

PT Term	Code
Hepatic haemorrhage	10019677
Hereditary haemorrhagic telangiectasia	10019883
Hip fracture	10020100
Humerus fracture	10020462
Hyphaema	10020923
Hypophosphataemia	10021058
Hyporeflexia	10021089
Ilium fracture	10021343
Impaired healing	10021519
Increased tendency to bruise	10021688
Injection site bruising	10022052
Injection site haematoma	10022066
Injection site haemorrhage	10022067
Intermenstrual bleeding	10022559
Internal fixation of fracture	10022576
International normalised ratio abnormal	10022592
International normalised ratio increased	10022595
Intracranial tumour haemorrhage	10022775
Intraventricular haemorrhage	10022840
Intraventricular haemorrhage neonatal	10022841
Keratomalacia	10023361
Kidney contusion	10023413
Kyphosis	10023509
Mallory-Weiss syndrome	10026712
Melaena	10027141
Menometrorrhagia	10027295
Mouth haemorrhage	10028024
Multiple fractures	10028200
Muscle haemorrhage	10028309
Muscle spasms	10028334
Muscular weakness	10028372
Musculoskeletal pain	10028391
Myalgia	10028411
Myocardial rupture	10028604
Nephritis haemorrhagic	10029132
Neuropathic arthropathy	10029326
Night blindness	10029404
Nipple exudate bloody	10029418

PT Term	Code
Nystagmus	10029864
Oesophageal haemorrhage	10030172
Oesophageal ulcer haemorrhage	10030202
Oesophageal varices haemorrhage	10030210
Oesophagitis haemorrhagic	10030219
Open fracture	10030527
Open reduction of fracture	10030682
Open reduction of spinal fracture	10030684
Ophthalmoplegia	10030875
Optic disc haemorrhage	10030919
Optic nerve sheath haemorrhage	10030941
Orbital haemorrhage	10031045
Osteomalacia	10031250
Osteoporosis	10031282
Osteoporotic fracture	10031290
Ovarian haematoma	10033263
Pancreatic haemorrhage	10033625
Pancreatitis haemorrhagic	10033650
Pathological fracture	10034156
Pelvic haematoma obstetric	10034248
Penile haemorrhage	10034305
Peptic ulcer haemorrhage	10034344
Pericardial haemorrhage	10034476
Perineal haematoma	10034520
Periorbital haematoma	10034544
Petechiae	10034754
Pharyngeal haemorrhage	10034827
Placenta praevia haemorrhage	10035121
Post abortion haemorrhage	10036246
Post-traumatic osteoporosis	10036315
Postpartum haemorrhage	10036417
Premature separation of placenta	10036608
Proctitis haemorrhagic	10036778
Prostatic haemorrhage	10036960
Prothrombin level abnormal	10037048
Prothrombin level decreased	10037050
Prothrombin time abnormal	10037057
Prothrombin time prolonged	10037063

PT Term	Code
Pulmonary alveolar haemorrhage	10037313
Pulmonary contusion	10037370
Pulmonary haemorrhage	10037394
Purpura	10037549
Purpura fulminans	10037556
Purpura neonatal	10037557
Purpura senile	10037560
Radius fracture	10037802
Rectal haemorrhage	10038063
Rectal ulcer haemorrhage	10038081
Renal haematoma	10038459
Renal haemorrhage	10038460
Respiratory tract haemorrhage	10038727
Respiratory tract haemorrhage neonatal	10038728
Retinal haemorrhage	10038867
Retroperitoneal haemorrhage	10038980
Rib fracture	10039117
Ruptured cerebral aneurysm	10039330
Scrotal haematoma	10039749
Senile osteoporosis	10039984
Short stature	10040600
Spinal compression fracture	10041541
Spinal fracture	10041569
Splenic haematoma	10041646
Splenic haemorrhage	10041647
Splinter haemorrhages	10041663
Sternal fracture	10042015
Stomatitis haemorrhagic	10042132
Stress fracture	10042212
Subarachnoid haemorrhage	10042316
Subarachnoid haemorrhage neonatal	10042317
Subcutaneous haematoma	10042345
Subdural haematoma	10042361
Subdural haematoma evacuation	10042363
Subdural haemorrhage	10042364
Subdural haemorrhage neonatal	10042365
Third stage postpartum haemorrhage	10043449
Thrombocytopenic purpura	10043561

PT Term	Code
Thrombotic thrombocytopenic purpura	10043648
Tibia fracture	10043827
Tongue haematoma	10043959
Tooth injury	10044043
Tooth malformation	10044046
Traumatic haematoma	10044522
Tremor	10044565
Ulna fracture	10045375
Umbilical haemorrhage	10045455
Upper gastrointestinal haemorrhage	10046274
Urinary bladder haemorrhage	10046528
Uterine haemorrhage	10046788
Vaginal haematoma	10046909
Vaginal haemorrhage	10046910
Varicose vein ruptured	10046999
Vascular purpura	10047097
Ventricle rupture	10047279
Vitamin A deficiency related conjunctival disorder	10047588
Vitamin A deficiency related corneal disorder	10047589
Vitreous haemorrhage	10047655
Vulval haematoma	10047756
Vulval haematoma evacuation	10047757
Withdrawal bleed	10047998
Wrist fracture	10048049
Xerophthalmia	10048221
Xerosis	10048222
Aneurysm ruptured	10048380
Atrial rupture	10048761
Myocardial haemorrhage	10048849
Nail bed bleeding	10048891
Spinal cord haemorrhage	10048992
Osteopenia	10049088
Fractured coccyx	10049164
Spinal epidural haemorrhage	10049236
Lip haemorrhage	10049297
Bone density decreased	10049470
Traumatic fracture	10049514
Anal haemorrhage	10049555

PT Term	Code
Urethral haemorrhage	10049710
Tumour haemorrhage	10049750
Pituitary haemorrhage	10049760
Shock haemorrhagic	10049771
Melaena neonatal	10049777
Tongue haemorrhage	10049870
Osteoporosis prophylaxis	10049904
Mediastinal haematoma	10049941
Cervical vertebral fracture	10049946
Lumbar vertebral fracture	10049947
Thoracic vertebral fracture	10049948
Cervix haematoma uterine	10050020
Cervix haemorrhage uterine	10050022
Urogenital haemorrhage	10050058
Application site bruise	10050114
Cerebral haemorrhage foetal	10050157
Spinal epidural haematoma	10050162
Spinal subdural haematoma	10050164
Application site purpura	10050182
Skin ulcer haemorrhage	10050377
Chronic gastrointestinal bleeding	10050399
Haematosalpinx	10050468
Scleral haemorrhage	10050508
Contusion	10050584
Lower gastrointestinal haemorrhage	10050953
Post procedural haemorrhage	10051077
Catheter site haemorrhage	10051099
Incision site haemorrhage	10051100
Puncture site haemorrhage	10051101
Parotid gland haemorrhage	10051166
Soft tissue haemorrhage	10051297
Carotid aneurysm rupture	10051328
Wound haemorrhage	10051373
Retinopathy haemorrhagic	10051447
Corneal bleeding	10051558
Haematoma infection	10051564
Testicular haemorrhage	10051877
Osteorrhagia	10051937

PT Term	Code
Urinary occult blood positive	10052287
Brain contusion	10052346
Large intestinal haemorrhage	10052534
Small intestinal haemorrhage	10052535
Meningorrhagia	10052593
Comminuted fracture	10052614
Induced abortion haemorrhage	10052844
Eyelid bleeding	10053196
Fracture displacement	10053206
Anticoagulant therapy	10053468
Traumatic haemorrhage	10053476
Vascular rupture	10053649
Growth retardation	10053759
Gastroduodenal haemorrhage	10053768
Cerebral haematoma	10053942
Vascular pseudoaneurysm ruptured	10053949
Epiphyseal fracture	10053962
Implant site haemorrhage	10053995
Vessel puncture site haemorrhage	10054092
Haemorrhagic tumour necrosis	10054096
Haemorrhoidal haemorrhage	10054787
Retroplacental haematoma	10054798
Hepatic haemangioma rupture	10054885
Pelvic haematoma	10054974
Pulmonary haematoma	10054991
Arteriovenous fistula site haemorrhage	10055123
Arteriovenous graft site haemorrhage	10055126
Arteriovenous fistula site haematoma	10055150
Arteriovenous graft site haematoma	10055152
Catheter site haematoma	10055662
Haemorrhagic transformation stroke	10055677
Haemorrhage	10055798
Haemorrhage coronary artery	10055803
Haemorrhage urinary tract	10055847
Postmenopausal haemorrhage	10055870
Haematoma muscle	10055890
Protein induced by vitamin K absence or antagonist II	10056243
Protein induced by vitamin K absence or antagonist II increased	10056247

PT Term	Code
Mediastinal haemorrhage	10056343
Anastomotic haemorrhage	10056346
Pituitary apoplexy	10056447
Intra-abdominal haematoma	10056457
Gastrointestinal ulcer haemorrhage	10056743
Body height decreased	10056812
Palpable purpura	10056872
Fracture debridement	10057147
Loss of proprioception	10057332
Ciliary body haemorrhage	10057417
Iris haemorrhage	10057418
Tonsillar haemorrhage	10057450
Ocular retrobulbar haemorrhage	10057571
Gastric varices haemorrhage	10057572
Fracture reduction	10057609
Cognitive disorder	10057668
Bloody discharge	10057687
Purpura non-thrombocytopenic	10057739
Peritoneal haematoma	10058095
Retroperitoneal haematoma	10058360
Spinal deformity	10058907
Thalamus haemorrhage	10058939
Putamen haemorrhage	10058940
Haemobilia	10058947
Acute haemorrhagic leukoencephalitis	10058994
Cullen's sign	10059029
Parathyroid haemorrhage	10059051
Papillary muscle haemorrhage	10059164
Intestinal haemorrhage	10059175
Haemorrhagic cyst	10059189
Adrenal haematoma	10059194
Infusion site bruising	10059203
Incision site haematoma	10059241
Intracranial haematoma	10059491
Haemorrhagic urticaria	10059499
Haemorrhagic ascites	10059766
Renal cyst haemorrhage	10059846
Anticoagulation drug level above therapeutic	10060320

PT Term	Code
Skin neoplasm bleeding	10060712
Mesenteric haemorrhage	10060717
Haematoma evacuation	10060733
Haemorrhagic ovarian cyst	10060781
Aortic rupture	10060874
Arterial haemorrhage	10060964
Cerebellar haematoma	10061038
Pelvic fracture	10061161
Genital haemorrhage	10061178
Haemorrhage foetal	10061191
Intra-abdominal haemorrhage	10061249
Large intestinal ulcer haemorrhage	10061262
Mucosal haemorrhage	10061298
Pelvic deformity	10061335
Scrotal haemorrhage	10061361
Traumatic intracranial haemorrhage	10061387
Upper limb fracture	10061394
Vitamin A deficiency eye disorder	10061412
Scrotal haematocoele	10061517
Small intestinal ulcer haemorrhage	10061550
Ulcer haemorrhage	10061577
Lower limb fracture	10061599
Coagulation factor IX level abnormal	10061770
Coagulation factor VII level abnormal	10061772
Coagulation factor X level abnormal	10061774
Occult blood positive	10061880
Fracture treatment	10061959
Haemorrhage neonatal	10061993
Intracerebral haematoma evacuation	10062025
Knee deformity	10062061
Tracheal haemorrhage	10062543
Tooth fracture	10062544
Bladder tamponade	10062656
Haemorrhagic diathesis	10062713
Thoracic haemorrhage	10062744
Naevus haemorrhage	10062955
Haematotympanum	10063013
Post procedural haematoma	10063188

PT Term	Code
International normalised ratio fluctuation	10063351
Circulating anticoagulant positive	10063576
Graft haemorrhage	10063577
Catheter site bruise	10063587
Pelvic haemorrhage	10063678
Implant site haematoma	10063780
Vulval haemorrhage	10063816
Implant site bruising	10063850
Uterine haematoma	10063875
Vessel puncture site bruise	10063881
Anal ulcer haemorrhage	10063896
Polymenorrhagia	10064050
Angina bullosa haemorrhagica	10064223
Thyroid haemorrhage	10064224
Skin haemorrhage	10064265
Umbilical cord haemorrhage	10064534
Haemorrhagic arteriovenous malformation	10064595
Breast haematoma	10064753
Tooth socket haemorrhage	10064946
Eyelid haematoma	10064976
Ulcerative keratitis	10064996
Coital bleeding	10065019
Haemophilic arthropathy	10065057
Spontaneous haematoma	10065304
Venous haemorrhage	10065441
Infusion site haematoma	10065463
Infusion site haemorrhage	10065464
Bronchial haemorrhage	10065739
Laryngeal haemorrhage	10065740
Ovarian haemorrhage	10065741
Spermatic cord haemorrhage	10065742
Ureteric haemorrhage	10065743
Vessel puncture site haematoma	10065902
Torus fracture	10066094
Avulsion fracture	10066184
Post procedural haematuria	10066225
Bone contusion	10066251
Lip haematoma	10066304

PT Term	Code
Impacted fracture	10066386
Basal ganglia haemorrhage	10067057
Liver contusion	10067266
Cerebral microhaemorrhage	10067277
Astringent therapy	10067372
Abdominal wall haematoma	10067383
Haemostasis	10067439
Myelomalacia	10067441
Bloody peritoneal effluent	10067442
Decreased vibratory sense	10067502
Intrapartum haemorrhage	10067703
Haemorrhagic erosive gastritis	10067786
Abdominal wall haemorrhage	10067788
Haemorrhagic hepatic cyst	10067796
Gastric occult blood positive	10067855
Aortic intramural haematoma	10067975
Aortic dissection rupture	10068119
Pharyngeal haematoma	10068121
Application site haematoma	10068317
Choroidal haematoma	10068642
Splenic varices haemorrhage	10068662
Umbilical haematoma	10068712
Bone density abnormal	10068789
Anorectal varices haemorrhage	10068925
Periprosthetic fracture	10069135
Abnormal withdrawal bleeding	10069195
Vaccination site haematoma	10069472
Vaccination site haemorrhage	10069475
Vaccination site bruising	10069484
Subgaleal haematoma	10069510
Paranasal sinus haematoma	10069702
Loss of anatomical alignment after fracture reduction	10069723
Intestinal haematoma	10069829
Lacrimal haemorrhage	10069930
Penile haematoma	10070656
Muscle contusion	10070757
Atypical femur fracture	10070884
Laryngeal haematoma	10070885

PT Term	Code
Subchorionic haemorrhage	10071010
Growth failure	10071095
Brain stem microhaemorrhage	10071205
Cerebellar microhaemorrhage	10071206
Procedural haemorrhage	10071229
Haemorrhagic vasculitis	10071252
Wound haematoma	10071504
Mesenteric haematoma	10071557
Post-traumatic punctate intraepidermal haemorrhage	10071639
Periorbital haemorrhage	10071697
Intraocular haematoma	10071934
Subretinal haematoma	10071935
Vitreous haematoma	10071936
Central nervous system haemorrhage	10072043
Fracture pain	10072132
Tooth pulp haemorrhage	10072228
Haemorrhagic thyroid cyst	10072256
Post transfusion purpura	10072265
Radiation associated haemorrhage	10072281
Atypical fracture	10072395
Subchorionic haematoma	10072596
Peripartum haemorrhage	10072693
Application site haemorrhage	10072694
Chronic pigmented purpura	10072726
Iliac artery rupture	10072789
Chance fracture	10073162
Brain stem haematoma	10073230
Penile contusion	10073352
Post procedural contusion	10073353
Eye contusion	10073354
Genital contusion	10073355
Cardiac contusion	10073356
Spleen contusion	10073533
Spinal subdural haemorrhage	10073563
Spinal subarachnoid haemorrhage	10073564
Bone marrow haemorrhage	10073581
Instillation site haematoma	10073609
Instillation site haemorrhage	10073610

PT Term	Code
Instillation site bruise	10073630
Epidural haemorrhage	10073681
Haemophilic pseudotumour	10073770
Osteochondral fracture	10073853
Neonatal gastrointestinal haemorrhage	10074159
Lymph node haemorrhage	10074270
Sacroiliac fracture	10074362
Gastrointestinal polyp haemorrhage	10074437
Traumatic haemothorax	10074487
Stoma site haemorrhage	10074508
Limb fracture	10074551
Spontaneous haemorrhage	10074557
Deep dissecting haematoma	10074718
Hyperfibrinolysis	10074737
Oral mucosa haematoma	10074779
Spinal fusion fracture	10074807
Arterial intramural haematoma	10074971
Eyelid contusion	10075018
Nasal septum haematoma	10075027
Administration site bruise	10075094
Administration site haematoma	10075100
Administration site haemorrhage	10075101
Internal haemorrhage	10075192
Activated partial thromboplastin time ratio abnormal	10075284
Activated partial thromboplastin time ratio fluctuation	10075286
Activated partial thromboplastin time ratio increased	10075287
Aponeurosis contusion	10075330
Cerebral aneurysm perforation	10075394
Grey Turner's sign	10075426
Medical device site bruise	10075570
Medical device site haematoma	10075577
Medical device site haemorrhage	10075578
Acute haemorrhagic ulcerative colitis	10075634
Carotid artery perforation	10075728
Aortic perforation	10075729
Lower limb artery perforation	10075730
Iliac artery perforation	10075731
Arterial perforation	10075732

PT Term	Code
Venous perforation	10075733
Cerebral artery perforation	10075734
Vertebral artery perforation	10075735
Basilar artery perforation	10075736
Renal artery perforation	10075737
Splenic artery perforation	10075738
Femoral artery perforation	10075739
Subclavian artery perforation	10075740
Superior vena cava perforation	10075741
Inferior vena cava perforation	10075742
Subclavian vein perforation	10075743
Iliac vein perforation	10075744
Femoral vein perforation	10075745
Mucocutaneous haemorrhage	10076048
Spinal cord haematoma	10076051
Haemorrhagic necrotic pancreatitis	10076058
Oral blood blister	10076590
Chest wall haematoma	10076597
Subarachnoid haematoma	10076701
Periventricular haemorrhage neonatal	10076706
Basal ganglia haematoma	10077031
Vein rupture	10077110
Surgical fixation of rib fracture	10077270
Periosteal haematoma	10077341
Haemorrhagic breast cyst	10077443
Oesophageal intramural haematoma	10077486
Vascular access site haemorrhage	10077643
Vascular access site haematoma[a]	10077647
Vascular access site rupture	10077652
Joint microhaemorrhage	10077666
Vascular graft haemorrhage	10077721
Vascular access site bruising	10077767
Bursal haematoma	10077818
Intestinal varices haemorrhage	10078058
Oral contusion	10078170
Extra-axial haemorrhage	10078254
Costal cartilage fracture	10078358
Lisfranc fracture	10078749

PT Term	Code
Traumatic intracranial haematoma	10079013
Retinal aneurysm rupture	10079121
Bronchial varices haemorrhage	10079163
Fracture blisters	10079423
Achenbach syndrome	10079562
Metaphyseal corner fracture	10079667
Anal fissure haemorrhage	10079765
Fracture infection	10079813
Subchondral insufficiency fracture	10079864
Eye haematoma	10079891
Haemorrhagic adrenal infarction	10079902
Peripheral artery aneurysm rupture	10079908
Paranasal sinus haemorrhage	10080108
Pseudofracture	10080404
Osteophyte fracture	10080550
Gastrointestinal vascular malformation haemorrhagic	10080561
Subgaleal haemorrhage	10080900
Maisonneuve fracture	10081343
Hypophosphataemic osteomalacia	10081362
Fothergill sign positive	10081749
Growth disorder	10081945
Puncture site haematoma	10081957
Puncture site bruise	10082035
Cerebral cyst haemorrhage	10082099
Pulmonary haemorrhage neonatal	10082194
Blood loss anaemia	10082297
Pathological fracture prophylaxis	10082364
Subendocardial haemorrhage	10082459
Acquired factor IX deficiency	10082747
Extradural haematoma evacuation	10082797
Pathological tooth fracture	10082930
Pharyngeal contusion	10083176
Anticoagulant-related nephropathy	10083346
Urinary bladder haematoma	10083358
Subcapsular hepatic haematoma	10083383
Subcapsular splenic haematoma	10083384
Subcapsular renal haematoma	10083385
Oral purpura	10083533

PT Term	Code
Orbital haematoma	10083565
Spinal fracture treatment	10083586
Bullous haemorrhagic dermatosis	10083809
Pancreatic pseudocyst haemorrhage	10083813
Immune thrombocytopenia	10083842
Haemangioma rupture	10084040
Vascular anastomotic haemorrhage	10084092
Intratumoural haematoma	10084177
Antiplatelet reversal therapy	10084904
Urinary occult blood	10084960
Omental haemorrhage	10085045
Haemorrhagic occlusive retinal vasculitis	10085070
Haemorrhagic gastroenteritis	10085136
Scleral haematoma	10085163
Jugular vein haemorrhage	10085298
Gastrointestinal anastomotic haemorrhage	10085369
Heavy menstrual bleeding	10085423
Abnormal uterine bleeding	10085424
Gallbladder haematoma	10085893
Haemorrhagic cerebellar infarction	10085944
Peripheral exudative haemorrhagic chorioretinopathy	10086195
Hypergammaglobulinaemic purpura of Waldenstrom	10086403
Intracranial haemorrhage neonatal	10086946
Hepatic artery haemorrhage	10087132

[a] The list of PTs in Appendix G was created based on MedDRA Version 25.0; as of MedDRA Version 26.0, LLT Peripheral artery haematoma has been changed from PT Peripheral artery haematoma to PT Vascular access site haematoma.